Hospital Library

MARCH 1941

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

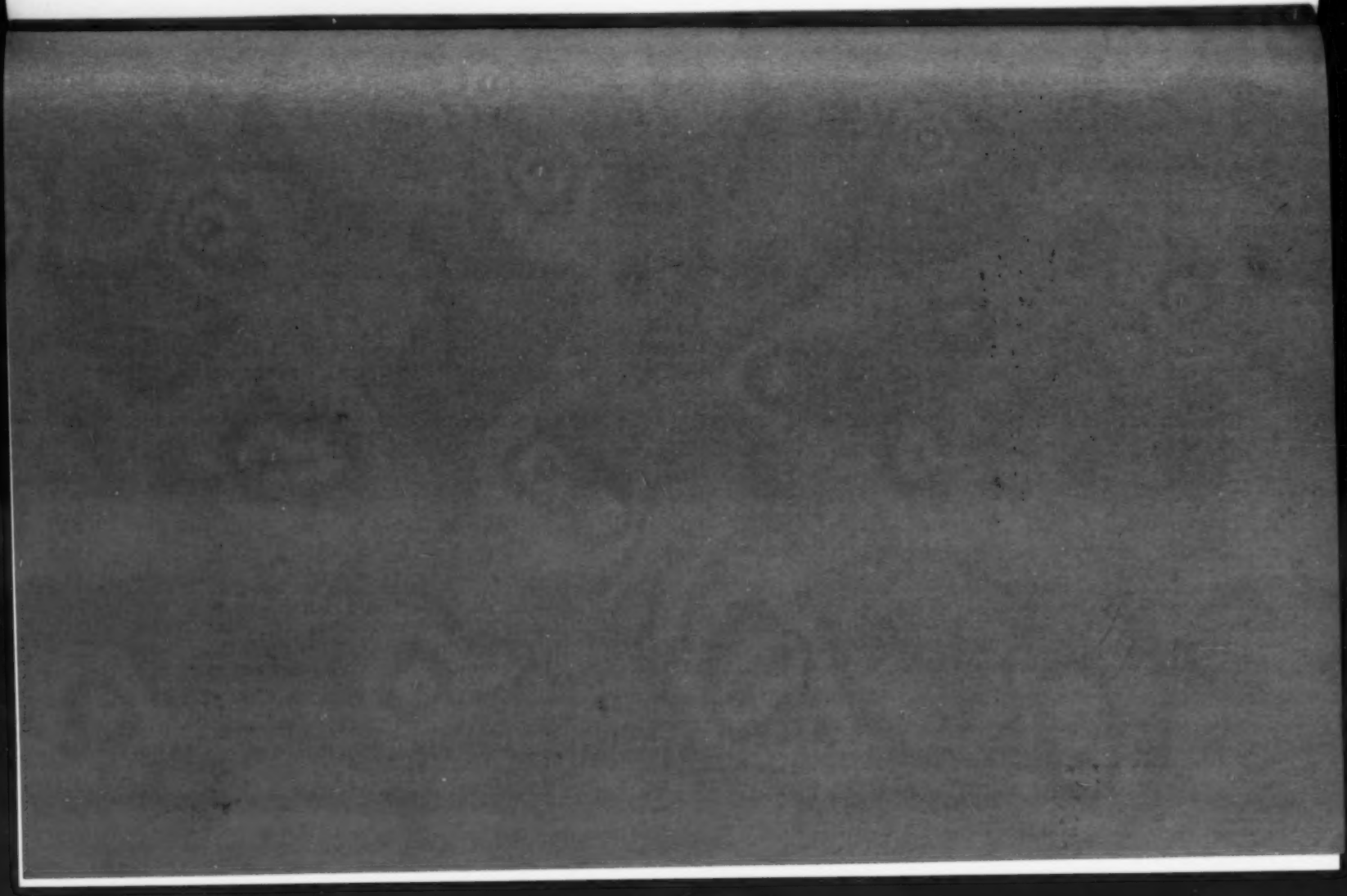
MAR 3'41

Original Articles

by

EDGAR V. ALLEN
HOBART A. REIMANN
NORMAN JOLLIFFE
MATHER CLEVELAND
FRANK L. MELENEY

ADDRESS OF THE PRESIDENT



SECOND SERIES MARCH 1941 VOL. 17, NO. 3

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

CONTENTS

Inaugural Address of the President of The New York Academy of Medicine 165
Malcolm Goodridge

Medical Aspects of Arterial Hypertension 174
Edgar V. Allen

Pneumococcal and "Virus" Pneumonia 187
Hobart A. Reimann

Newer Knowledge of the Vitamin B-Complex . . . 195
Norman Jolliffe

Osteomyelitis and Pyogenic Infections of Joints . . . 205
Mather Cleveland

The Prevention and Treatment of Infection in Wounds both Operative and Accidental 221
Frank L. Meleney

Library Notes:

Recent Accessions to the Library 242

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

Published monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York

Entered as second-class matter, February 3, 1928, at the Post Office at New York, N. Y., under the Act of August 24, 1912. Subscription, United States, Canada and Cuba, $3.00; all other countries, $4.00 a year. Single copies, 50c.

OFFICERS AND STAFF OF THE ACADEMY

1941

President

MALCOLM GOODRIDGE

Vice-Presidents

RUFUS I. COLE — I. OGDEN WOODRUFF — HENRY CAVE

Treasurer

BERNARD SACHS

Assistant Treasurer

RODERICK V. GRACE

Recording Secretary

JAMES RALPH SCOTT

Trustees

GEORGE BAEHR
ARTHUR F. CHACE
CARL EGGERS
*MALCOLM GOODRIDGE
SHEPARD KRECH
JAMES ALEXANDER MILLER
HAROLD R. MIXSELL
WALTER L. NILES
EUGENE H. POOL
*BERNARD SACHS
*JAMES RALPH SCOTT
FREDERIC E. SONDERN
CHARLES F. TENNEY

Council

The President — The Vice-Presidents — The Trustees
The Treasurer — The Recording Secretary
The Chairmen of Standing Committees

Director

HERBERT B. WILCOX

Librarian

ARCHIBALD MALLOCH

Executive Secretary
Public Health Relations Committee
E. H. L. CORWIN

Executive Secretary
Committee on Medical Education
MAHLON ASHFORD

Executive Secretary, Committee on Medical Information
IAGO GALDSTON

Library Consultants

LAURA E. SMITH — B. W. WEINBERGER — ARNOLD C. KLEBS

Legal Counsel
FRANK L. POLK, ESQ.

EDITORIAL BOARD

JEROME P. WEBSTER, *Chairman*

ALFRED E. COHN — ROBERT F. LOEB — PHILIP VAN INGEN
EUGENE F. DUBOIS — ARCHIBALD MALLOCH — KARL VOGEL
MAHLON ASHFORD, *Editor*

* Ex-officio

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

MARCH 1941

INAUGURAL ADDRESS OF THE PRESIDENT OF THE NEW YORK ACADEMY OF MEDICINE*

MALCOLM GOODRIDGE

WHAT IS THE NEW YORK ACADEMY OF MEDICINE?

FIRST, let me express my appreciation of the great honor which has been conferred upon me by the Fellows of The New York Academy of Medicine, in re-electing me their President.

Two years ago, I avowed a full understanding of my responsibility. My responsibility continues; it has even increased in the two years in which I have been in office, and, while I may not have the same awareness today of my inadequacy that I had then, my humility is undiminished and my enthusiasm has progressed. Perhaps this is a happy combination, humility and enthusiasm.

I have been impressed, during my two years in office, by the fact that the public knows really little of what the Academy is, and what its accomplishments have been.

Why should this be so? In searching for the reason, I have concluded that it is chiefly because we, as individual physicians who form the Fellowship of the Academy, have an obsession against advertising; it is a traditional violation of medical ethics to advertise, and we have

* Given January 2, 1941 at the Annual Meeting of The New York Academy of Medicine.

carried this aversion into our administration of the Academy.

I feel that this is a mistaken philosophy; I am sure it is wise, even necessary, for the public to know what we are doing.

Two years ago, I told something of the history of the Academy. Tonight, I am going to try to tell you what the Academy *is*.

After all, what *is* The New York Academy of Medicine? It might be defined as an association of physicians, incorporated under the laws of the State of New York, June 23, 1851, for the purpose of promoting the advancement of medical science by such means as to them shall appear expedient and proper, and now occupying the premises at 2 East 103d Street; and, even if I went no farther than that, it would be news to *most* people.

To begin with, I should say there is a general misunderstanding concerning the relationship of the Academy to organized medicine. There is really *no* relationship, except insofar as individual Fellows of the Academy are members of the medical societies in the county, state, and country which make up organized medicine. We as individuals are vitally interested in the affairs of the physician, in his training and ethics, in his relationship to the public, and in his economic welfare.

The other day, I reread the Inaugural Address of a past President of the Academy who is still living, Dr. Samuel W. Lambert. He said, "The New York Academy of Medicine is not a local medical group. It has become a national institution." And, with rare foresight and vision, he said of our new building, "This building is an asset of which we may be proud, but it is also a liability which calls for increased expenditures now and in the future. . . . No one must forget that the future will always call for increasing endowments to meet the necessary expenses of the present work and also expand into the unknown and compelling activities of the future. . . . This academy, like every educational institution, must go on to new fields of work or retrograde and slip from its position of prominence." This address of Dr. Lambert's was delivered in 1927, a short time after we moved out of our old building on West 43rd Street, where the Academy was in large measure self-sustaining and supported by membership dues.

Curiously enough, one of the difficulties in which we now find ourselves is due, in part at least, to the financial support of the Foundations which endowed us with large sums of money, stimulating us to go forward with projects we had not previously undertaken. The de-

mands on us increased in direct proportion to the service we rendered, that is, as we improved our service, the demands grew. With the aid of the Foundations, we have come this far.

Let me review briefly for you what the several departments of the Academy of Medicine have done and are doing. Please remember, I cannot in the short time available this evening tell the whole story of our Library and of the Standing Committees of the Academy, nor, in discussing the various committees shall I make any attempt to arrange them in the order of their importance. I am convinced this could not be done under any circumstances, for, with the Library as the hub, each department is a spoke in the wheel, of equal strength, and moving with equal velocity in any given direction.

Do you know that our Library is regarded by the Public Library of New York as the natural repository of medical books, and that it is particularly rich in books on medical biography and the history of medicine? And do you know that in 1939 the Academy Library served more than six times as many readers as any other medical library in the country, and that of these readers *eighty-seven per cent* were *not* Fellows of the Academy?

Do you know that in 1939, through our interlibrary loan service, we loaned 3,040 volumes to 156 libraries, at an actual cost to the Academy of $1,520, while the books borrowed by the Academy for the use of its Fellows totaled but seven volumes, at a cost of three dollars and a half?

Do you know that the bibliographical service furnished by our Library is one of but three such medical services in this country, and that the charges for this service do not nearly cover the cost? This, of course, represents a valid contribution to medical scholarship.

Do you know we have a card index to our Library Portrait Catalogue, with some 47,000 cards, representing 86,000 portraits of 30,000 individuals? This list is in constant use, and the Catalogue is unique in medical library service. Reproduction of library material by photograph, photostat, and microfilm served 1,381 clients in 1939.

Do you know what the Union List of Serials is? It contains the periodical holdings of hundreds of libraries in the United States and Canada, and up to 1925 it contained 75,000 entries. Since 1930, there has been an annual supplement, published quarterly. The cost of the original list was $70,000, of which the Academy paid $1,800, in addi-

tion to the cost, $2,850, of listing its holdings, and we contribute about $500 a year toward meeting the cost of the annual supplement. Obviously, a list of this kind has immense value as a reference book to the entire medical world.

Do you know that our Library has given duplicates to libraries in other countries, to Japan, in 1924, to replace losses suffered in the earthquake, to China, from 1932 to 1940, to replace losses due to the Japanese invasions, to Hungary, to Fiji, and to Chile? Do you know that in 1939, through the Exchange Service of the Medical Library Association, we gave to 272 libraries in the United States and Canada 19,834 duplicates, and that the cost of handling this material was carried by the Academy, for the benefit of other libraries?

Do you know our Library has a collection of hospital and health reports, medical school announcements, and medical government documents from all over the world that is second to none?

And do you realize that these documents are costly to gather, to catalogue, and to store?

The Committee on Public Health Relations of the Academy is approaching its thirtieth birthday, having been in existence since 1911. Do you know that this Committee was entirely responsible for the transfer of quarantine of the Port of New York from the jurisdiction of the State to that of the Federal Government? And that it worked for the cleaning up and prevention of further pollution of the waters around the City of New York; that it made studies and recommendations to effect more efficient handling of city refuse; that it worked for improvement in housing conditions through recommendation of enactment of a new Tenement House Law in 1929, and for the correction of apparent maladjustments in the administration and application of the Workmen's Compensation Law; that it studied procedure in children's and domestic relations courts, with the result that the number of children brought before the bench has been reduced by half; that it worked for established standards for physical examination of factory workers from fourteen to sixteen years of age; and for periodic examination of school teachers, for improved conditions for school children in the matter of nutrition, schoolroom lighting and ventilation, and provisions for handicapped children; for better food and drug laws, and for the protection of the public from fraudulent advertising; that it initiated the movement for the establishment of a uniform nomenclature of dis-

ease; that it appointed a committee, back in 1927, to consider the need of a medical and public health museum, and today there has been established such a museum, the American Museum of Health; and that it has worked for the establishment of an Institute of Forensic Medicine? That studies as to clinical diagnosis for use in cardiac diseases, the control of venereal diseases and the disposition of carriers, and the care of mental defectives have been carried on by this Committee; and that it was asked to study the social and clinical aspects of marihuana poisoning, with the coöperation of the Departments of Health, Welfare, and Police? And that it has worked for more adequate hospital facilities for tuberculosis and contagious diseases? And that it participated in the study which resulted in an appreciable reduction in diarrheal deaths in the newborn?

A subcommittee of the Public Health Relations Committee worked for a number of years, searching out the causes of maternal mortality and making recommendations which effected a reduction of 50 per cent of unnecessary deaths within five years after the publication of their report, six years ago. Do you know who the members of this subcommittee were? I doubt if many Fellows of the Academy could name them.

Do you know that as long ago as 1927, the Committee on Public Health Relations made certain recommendations to the Commissioner of Health, in order to safeguard the patient, the agency, and the professional donor, in the use of blood transfusion; and that these recommendations were adopted, placing agencies and professional donors under the control of the Department of Health; and that in 1930, under the motivating force of this same committee of the Academy, the Blood Transfusion Betterment Association was formed? And that this Association is now coöperating with the New York Chapter of the American Red Cross, in centralizing blood donors for the collection of blood plasma for wounded and shocked soldiers and civilians of Great Britain, and incidentally laying the foundation for the use of plasma in our own defense? Sacramento 2-8950, which you see frequently nowadays, associated with pleas for blood plasma for Britain, is the telephone number of the clearing house for plasma volunteers, and that clearing house is located on the fourth floor of this, our Academy building, in space contributed by the Academy for such use.

Bear in mind that one of the most important relationships of the

Academy to the public is the education of the doctor. How many of you ever stop to consider just how much the Committee on Medical Education does in this direction, arranging the scientific programs of the eight Stated Meetings which are held each year, arranging for twenty lectures given on Friday afternoons on subjects of current importance to physicians, and five lectures on Wednesday afternoons devoted to problems which the general practitioner is apt to encounter in the field of Obstetrics? And let me add that *all* of the Stated Meetings and the Wednesday Afternoon and Friday Afternoon Lectures are open to the entire medical profession.

Perhaps one of the most important functions of this Committee is the arrangement of the Graduate Fortnight, which is held in October of each year. During this Fortnight, a subject of live general medical interest is treated, and medical men from various cities, states, and countries enroll. The Fortnight consists of evening lectures by men from all parts of the country, recognized authorities in their particular fields; morning panel discussions; afternoon clinics in the various hospitals of this city; and a large exhibit of various items pertinent to the subject of the Fortnight. Last year, the subject was "Infections." The year before, it was "The Endocrines." Next October, it will be "Cardiovascular Diseases, including Hypertension."

The Committee maintains a Bureau of Clinical Information, concerning opportunities for medical instruction or education throughout the country, and publishes a daily bulletin of surgical operations in various clinics of the city, a daily bulletin of meetings, lectures, conferences, and hospital rounds, and a bulletin of clinical and pathological conferences and special rounds in the hospitals of New York.

It also coöperates with the Department of State of the United States, in guiding medical scientists and students from South American countries on their arrival in New York.

Separate from the Committee on Medical Education, but closely affiliated with it, The New York Academy of Medicine publishes a monthly medical journal called the Bulletin, under the authority of a duly appointed editorial board.

If you know that the Committee on Sections is a Standing Committee of the Academy, you are better informed than most, for some of the members of the Council did not know it until about a year ago; and yet, this is one of the most important features of our organization. The

chairman of this Committee is appointed by the Council from among the three Vice-Presidents of the Academy. There are eleven sections in all, ten scientific, each concerned with some special field of medicine, and one historical and cultural section. Each of these sections meets once a month, and various topics of importance in the medical world are discussed freely.

I would like to emphasize the fact that these Section meetings also are open to all members of the medical profession.

Finally, we have a Standing Committee known as the Committee on Medical Information, of very great importance, because it acts, as its name connotes, as a link between the entire field of medicine and the public.

Let me show you just how effective it is in this respect. The press has made a thousand inquiries, and there have been as many as two thousand from individuals, lay organizations, and commercial organizations within the last year. The answering of such inquiries has an extremely important bearing on the health of the community, and the work of this Committee is a feature of the Academy's work which the public knows almost nothing about. The people do not realize that they are being protected against misrepresentation in commercial advertising through the influence of this Academy activity.

Under the aegis of this Committee, a series of "Lectures to the Laity" is given every year, on topics of interest to the general public, which the Columbia University Press publishes in book form under the title, "The March of Medicine." The average attendance at the last series was 779.

A year ago, under a fellowship grant from the Rockefeller Foundation, the Committee made a study of radio broadcasting of medical information.

Under the direction of the Committee, a radio period, known as "Highways to Health," may be heard over Station WABC every week in the year.

The various committees of the Academy are bound together in a common interest. As evidence of this, let me cite an example: One of the most important of last year's conferences was held under the auspices of the Committee on Medical Information, the "Health Education Conference," which brought together public health officers, voluntary health organizations, and medicine, as such, on the one hand,

and the press and radio, chief distributors of news, on the other.

The press of this city has drawn attention editorially many times to the part which The New York Academy of Medicine plays in the city's life, its friendship to the community, and its service to the public.

The Library figures give us a fair index of Academy growth in all of its departments, since we moved, fifteen years ago, from 43rd Street into our present building. The total items in the Library, books, catalogues, pamphlets, periodicals, and theses, increased by 70 per cent; the readers using our Library increased during this same period of time by 185 per cent, while the Library personnel increased by but 60 per cent.

In 1928, the Library expenditures were almost exactly the same as the budgetary allowance for the coming year.

I fear I have burdened you with a dull story, told in facts and figures, but for some time it has been apparent to me that we must let the Fellows of the Academy and the public know what we are doing and what it costs to maintain this organization.

I regret the lack of the gift of expression which would enable me to give you an idea of the enthusiasm with which the personnel of the Academy staff carries on in spite of some discouraging handicaps. I cannot find words which would adequately set forth my admiration for the devotion of the Fellows of the Academy who have given so much of their time, energy, and wisdom for the advancement of medical science and for the betterment of the public welfare.

A year ago I called attention to the Academy deficit for the year ending December 31, 1939. Perhaps many of you do not yet know that a deficit of some eighteen thousand dollars in that year was met through the generosity of Mr. Bernard M. Baruch.

During the past year the growth of the Library has been retarded and every department of the Academy has been shorthanded because your Budget Committee was compelled to make its allowance nearly forty-five thousand dollars less than the budgetary requests.

Make no mistake about it, we are determined to go forward. We shall resist to the utmost any thought of turning back. But neither the fervor of the Fellows of the Academy nor its understaffed personnel can do it all. Unfortunately, we are not in a position to shoulder all of the financial responsibility for the future.

If I have been in the least convincing, in relating my story of the Academy, its triumphs as well as its trials and tribulations, then I must

have demonstrated at the same time that we are worthy of liberal financial support.

The Library needs more stack space. We own the ground on which an addition might be built for such use. The plans are drawn, not only for increase in the space required to house our books, but also for such rehabilitation of our present available space as will permit us to meet the tremendous increase in the demands which have been made on the Library in recent years.

A committee of Academy Fellows, under the chairmanship of Dr. Harold R. Mixsell, was formed early in the past year to raise the necessary funds to permit us to go forward and later to add to Academy endowment. A plan was adopted, under which we seek to raise $550,000 immediately, for the structural changes in the Library which I have already mentioned and for greatly needed support of our annual budget. It is our hope that in five years we may in addition increase our endowment fund by $1,250,000, so that there may be no interruption of Academy activities.

A suggestion made by Dr. Mixsell's committee, I am happy to announce, has become effective. A Lay Council or advisory committee has been formed as a permanent feature of the Academy organization. The following gentlemen have consented to serve in this Council: Messrs. Walter S. Gifford, Chairman; Arthur M. Anderson, George Blumenthal, Lewis H. Brown, Clinton H. Crane, Marshall Field, Joseph M. Hartfield, David M. Heyman, Philip W. Lennen, George W. Merck, and Edward L. Shea. They have met with Dr. Mixsell's committee individually and collectively, and have already rendered inestimable service in terms of helpful advice.

Let me say, in closing, that we have no delusions concerning our importance, and no illusions with regard to our accomplishments. What we have done in the past will give you some conception of what we are today. Our hope and ambition in matters concerning the public health and medical education are endless.

MEDICAL ASPECTS OF ARTERIAL HYPERTENSION*

EDGAR V. ALLEN

Division of Medicine, Mayo Clinic, Rochester, Minnesota

A DISCUSSION such as this should begin logically with a definition of what constitutes normal blood pressure, for unless we know the value for normal blood pressure we cannot know where normal blood pressure ends and hypertension begins. We cannot find out by averaging the blood pressure of a large group of patients. Statisticians are fond of pointing out that the average height of a population half of whom are 6 feet tall and half of whom are 5½ feet tall is 5 feet and 9 inches. Yet there is not an individual in the group who has that height. Averaging blood pressures of a large group of patients will not allow us to conclude accurately what constitutes normal blood pressure. If one averages all of the figures, the figure for normal blood pressure will be too high and if one excludes frankly hypertensive values he is guilty of deciding beforehand the answer which he sought by such a study. Insurance figures do not help much either, for frequently the agent will not send to the insurance office the application of a candidate for insurance who appears to have hypertension. Also, the old rule that the normal systolic blood pressure is the age of the patient added to 100 is fallacious, for it is unquestionably true that the normal blood pressure of adults does not increase with age. The rather arbitrary upper limits of 140 mm. of mercury for normal systolic blood pressure and 90 mm. of mercury for normal diastolic blood pressure constitute a fairly adequate basis for determining normal blood pressure. However, recent studies of development of blood pressure and of survival of subjects whose blood pressures have been repeatedly observed indicate that the figure 140/90 is not the upper limit of normal blood pressure but indicates instead early hypertension. My associate, Hines,[1] has shown that in 70 per cent of patients who have blood pressures of 140/90 or slightly less, hypertension develops in twenty years, whereas

* Read October 3, 1940 before the Stated Meeting of The New York Academy of Medicine.

in only 3.6 per cent of those who have pressures of less than 120/85 does hypertension develop. He has also shown that, of those whose diastolic blood pressures are less than 85, hypertension develops in only 3.6 per cent whereas, of those whose diastolic blood pressures are 85 to 90, hypertension develops in 65 per cent. From a study carried out over a period of years, Robinson and Brucer[2] concluded that normal systolic blood pressure is between 90 and 120 mm. of mercury and the normal diastolic blood pressure is between 60 and 80 mm. of mercury. It is probable then that 120/80 is the upper limit for normal blood pressure. It is customary for physicians to attribute to the excitement of examination rather minor increases in blood pressure, as for example 145/95, and to be relieved when on subsequent examination the pressure is found to be lower, for example 130/80. However, evidence indicates that the patient whose pressure is 145/95 initially is indeed hypertensive, for were he not in fact already hypertensive, the stimulus of clinical examination would not cause an increase in his blood pressure to even such a relatively low value as 145/95.

The mechanism by which blood pressure is elevated in essential hypertension is well known. There exists throughout the body an increased resistance offered to the flow of blood through arterioles. In the early stages of hypertension this constriction of arterioles is easily reversible and during sleep or as a result of sedation the blood pressure returns to normal, indicating relaxation of arterioles. However, in most cases as time passes, this reversibility is lost and rest and sedation do not cause the blood pressure to return to normal. This failure of reversibility is commonly credited to organic changes in the arterioles. The argument about which comes first, the hen or the egg, has had a counterpart in consideration of hypertension. It seems quite clear now that organic changes in arterioles and arteries result from hypertension. There is little or no reason to believe that organic changes in arterioles (excepting perhaps those in the kidneys) precede hypertension or contribute to development of it in the early stages of this condition.

There are two chief hypotheses as to the cause of arteriolar constriction in hypertension. Some believe that this state is a direct result of overactivity of the sympathetic nervous system, causing widespread arteriolar constriction. There is much evidence which cannot be reviewed here to support this contention. A second hypothesis is that chemical substances circulate in the blood and produce vasoconstriction.

A variation of this hypothesis is that overactivity of the sympathetic nervous system causes arteriolar constriction in the kidneys, inducing release from them of a chemical, vasoconstrictive substance which in turn results in widespread arteriolar constriction and hypertension. However, such substances have not yet been demonstrated in essential hypertension. Since the excellent work of Goldblatt[3] and many others, there has been a tendency to assume that essential hypertension originates in the kidneys but there is no evidence, other than reasoning, that this is true. Most thoughtful students consider the cause of arteriolar constriction in hypertension to be uncertain at the present time.

It is now well known that hypertension of man indistinguishable from essential hypertension may be produced by unilateral renal lesions and that when a diseased kidney is removed surgically the blood pressure may return to normal. Barker and Walters[4] have demonstrated this in an excellent manner. Unfortunately, such renal lesions are found very unusually in hypertension. While I do not have the exact figures, my impression is that a lesion of a kidney which is responsible for hypertension can be demonstrated less than once in 300 cases. Nevertheless, a thorough study of a patient with essential hypertension must include urographic examination, for occasionally we see a patient who has neither unusual blood cells in the urine nor a history suggesting infection or stone in the urinary tract but who has atrophic pyelonephritis to which hypertension is secondary. Interestingly, Hines and Lander[5] have shown that hypertension seldom develops among patients who have atrophic pyelonephritis unless they had high normal blood pressures before pyelonephritis developed. This suggests that the substratum of hypertension must be present before pyelonephritis can provoke hypertension. It suggests also that pyelonephritis is only one of several specific stimuli which can cause hypertension. It is my impression that occasional demonstration of a renal cause for hypertension of man does not prove that all or most of essential hypertension is renal in origin but only that renal hypertension has been mistaken occasionally for essential hypertension.

One impressive feature of essential hypertension is the inheritance of it. It may seem strange that an individual can inherit a disease which does not become evident until middle adult life but there are examples of other conditions which occur similarly. Baldness, cerebellar atrophy, muscular dystrophies and atrophies may affect members of certain

families but not become apparent until after adolescence. Moreover, latent evidence of hypertension may be present early in life. Hines[6] has shown that excessive responses of blood pressure to a standard stimulus occur in about 18 per cent of healthy school children who have normal blood pressure. This is approximately the incidence of hypertension among adults. There is yet only incomplete but none-the-less suggestive evidence that of all subjects with normal blood pressure hypertension develops only among those whose blood pressure increases excessively when a hand is immersed in ice water or as a result of some other standard stimulus. In other words, even in childhood there may be occult evidence of hypertension. Coming events cast their shadows before.

Almost 95 per cent of patients with hypertension have a family history of cardiovascular disease. Ayman's[7] study shows that the incidence of elevated blood pressure in families in which both parents had normal blood pressure was only 3 per cent. If one parent had hypertension, the incidence of hypertension among the children was 28 per cent and when both parents had hypertension the respective figure was 45 per cent. The hereditary factor is well shown by the study of Hines,[8] which indicates that the substratum of hypertension is inherited and is apparent before hypertension develops.

If the physician bears in mind that hypertension may result from a number of causes, he need not overlook a specific cause for elevation of the blood pressure. He must consider coarctation of the aorta, nephritis, obstruction to the free flow of urine, Cushing's syndrome, tumors of the suprarenal glands, the kidneys, or the ovaries, and pyelonephritis. However, these conditions are almost always obvious or very uncommon. There is actually little value, and only interest, in differentiating chronic nephritis with hypertension from essential hypertension with renal involvement. The great majority of cases of hypertension are of the essential type, and ordinarily differential diagnosis is not difficult or it is unimportant.

The importance of hypertension as a problem of health needs emphasis. High blood pressure is both a common disease and a serious one. Indeed, it appears to be more common and more deadly than cancer. At the Mayo Clinic, each year, we encounter from 5,000 to 6,000 patients who have definite hypertension. According to estimates of the Metropolitan Life Insurance Company cardiovascular-renal dis-

eases will kill 600,000 people in the United States in 1940: that is, they will kill four times as many people as cancer will. Apparently, hypertension accounts for from a half to three-fourths of all deaths referable to cardiovascular-renal disease, and thus is from two to three times as deadly as cancer. About a fourth of all deaths of individuals past fifty years of age is referable to hypertension.

The classification of essential hypertension is valuable in prognosis. Keith, Wagener and Barker[9] have shown that the mortality in hypertension, groups 1 and 2, is 30 and 42 per cent, respectively, in four years from the time of their diagnosis, whereas, for a similar period, the mortality of hypertension, group 3, is 78 per cent and in group 4, it is 98 per cent. Among subjects who have systolic blood pressures of about 170 mm. of mercury, the relation of actual mortality to expected mortality according to insurance statistics is as 219.6 to 100; among those patients whose systolic blood pressures exceed 200 mm. of mercury, the actual mortality is to the expected as 827.5 is to 100. For individuals more than forty years of age, systolic blood pressure ranging from 35 to 44 mm. in excess of normal increases the expected mortality two and a half times. Such a slight increase in blood pressure as that represented by the figures 170 to 174, systolic, and 106, diastolic, expressed in millimeters of mercury, increases the expected mortality two and a half times.

Many physicians appear to be misled by the observation that an occasional patient survives hypertension for many years. They may then believe that hypertension in general is not very serious. Such an attitude is wishful in part, for few physicians like to face the fact that there is no routinely effective treatment for hypertension. If the physician believes that hypertension is not a serious disease, failure to treat it satisfactorily will not be so disappointing as it will be if he realizes the importance of the condition. This belief in the benignity of hypertension neglects to take into account repeated observations such as those written in the preceding paragraph: namely, that hypertension usually is a serious disease which terminates the lives of those it afflicts within a relatively short span.

Another cause for concern is the apparently decreasing age at which hypertension endangers the lives of those who are afflicted with it. This is a clinical impression based on the repeated observations that hypertensive members of a third generation die earlier than hyperten-

sive members of the second generation of the same family, and that those of the second generation die earlier than those of the first generation, apparently all from hypertension. Not uncommonly on questioning, the physician finds a situation similar to the following: the grandfather died at seventy-two years of age of "stroke;" the mother died at sixty of "Bright's disease" and the son, aged thirty-five years, is seriously ill from hypertension, which probably will terminate his life within a few months.[10] It appears that the incidence of hypertension in the general population is increasing but the evidence is not conclusive. Among patients at the Mayo Clinic it increased from about 2 per cent in 1919 to about 6 per cent in 1937. Estimates of the Metropolitan Life Insurance Company indicate that the mortality from cardiovascular-renal disease in the United States will increase from 600,000 in 1940 to 1,200,000 in 1960. Perhaps this is a result of our modern life.

During the past few years there has been much progress in the production of hypertension experimentally and in understanding of the mechanism by means of which the blood pressure is elevated in such experiments. A prominent example is the notable achievement of Goldblatt, who produced elevation of the blood pressure in animals by diminishing the blood supply to the kidneys. For these experiments, in which he produced a condition in animals closely resembling essential hypertension of man, Goldblatt received the Phillips Memorial Prize at the meeting of the American College of Physicians two years ago. I do not wish to detract from the excellent work that has been done on experimental hypertension and allied studies; rather, I wish to commend such work as being praiseworthy evidence that advances are occurring in a field of medicine in which little progress has been made until recently. I feel, however, that I shall not detract from this excellent experimental work if I indicate that it has helped only slightly the clinician who must attend patients who have hypertension. Up to the present time the only clinical benefit has been the knowledge that occasionally removal of a diseased kidney may cause blood pressure to return to normal and limited evidence that renal extracts may reduce blood pressure.[11]

Medical Treatment

Since hypertension is produced by increased resistance offered to the flow of blood through the arterioles, the specific need in medical

treatment is a preparation which will restore arteriolar resistance to normal and which will not produce harmful or unpleasant side effects. Unfortunately, such a preparation is not available now.

It is well to state herein that the belief, which persists stubbornly, that it is inadvisable to lower blood pressure in the presence of essential hypertension has no foundation in fact. In my experience with uncomplicated hypertension vital functions continue normally when blood pressure is reduced and I doubt that reduction of blood pressure in itself is harmful. I believe that such a reduction is highly desirable in uncomplicated hypertension.

It has been shown repeatedly that blood pressure is not static but is labile. This is particularly true in the presence of hypertension, when the blood pressure fluctuates greatly. Hines and I[12] have shown that if the systolic blood pressures of a group of patients in the clinic were more than 200 mm. of mercury, subsequent readings in the hospital would show that the systolic blood pressure decreased an average of about 50 mm. of mercury and that the average for the diastolic blood pressure decreased about 35 mm. of mercury, when no specific treatment was administered.

If all physicians who wrote of reduction of blood pressure as resulting from some specific method of treatment would determine the blood pressure of their patients hourly for twenty-four consecutive hours, they would not err in attributing to the treatment those reductions in blood pressure which occur without specific cause. There can be but little doubt that the popularity of many remedies is based on observation of diminution of blood pressure, a diminution which has occurred spontaneously and has not resulted from a specific remedy. Recently Kapernick,[13] working with me, has studied extensively the effects of a number of compounds on blood pressure. The blood pressure was determined at least twice daily on several groups of patients confined to a state hospital. After a control period of a week during which no medicine was given, various remedies were tried. The conclusion was that padutin, phenobarbital, hepvisc, iocapral, allimin, erythrol tetranitrate, aminophylline, theominal and theobromine do not reduce blood pressure significantly. Similar studies carried out in England[14] have shown similar results. A large number of remedies were found to be less valuable in reducing blood pressure than placebos were. There is much hope that renal extracts will prove to have clinical

value but at the present time results are uncertain although very encouraging.[11] Renal extracts are not as yet available for clinical use.

Potassium sulfocyanate has been used in the treatment of hypertension for several years.[15, 16] A relatively recent and important advance has been determination of the concentration of the cyanates in the blood by Barker.[17] The amount of this drug to be administered orally should be determined by frequent calculations of the concentration of cyanates in the blood.[18] The concentration in the serum should range between 8 and 14 mg. in each 100 cc. of blood. As little as a total of 5 grains (0.3 gm.) a week, or as much as 5 grains (0.3 gm.) three times daily, of potassium sulfocyanate, depending of course on the individual patient, must be administered to cause the aforementioned concentration in the blood. I give my patients 6 grains (0.4 gm.) daily to begin with and determine concentration of cyanates in the blood in one week. Subsequent dosage and the frequency of determination of concentration in the blood depend on individual responses. When the dosage is stabilized, determination of the blood cyanates every three to four weeks is adequate. Many physicians who cannot use large laboratories object to the use of cyanates because they have trouble obtaining an analysis of blood. Actually the technique is no harder than is the determination of urea in the blood and any technician can learn it. A kit* for office determination of cyanate in the blood is available. While the method includes matching colors, it has been in my experience fairly satisfactory except that the values found are likely to be higher than values determined chemically.

Such symptoms as headache, insomnia and nervousness may be relieved by treatment with cyanates. Fatigue, weakness, increasing nervousness, dermatitis, nausea, vomiting, anemia and enlargement of the thyroid gland may occur, even if administration of the drug is well controlled.[19] Weakness and fatigue may occur early in the course of adequate treatment, but usually they disappear as medication is continued. After five to ten years of treatment, elderly patients who have severe grades of hypertension may have anemia, emaciation and muscular wasting but it is not clear whether these conditions result from cyanate therapy or from hypertension itself. If the concentration of cyanates in the blood is too great, lethargy, mental confusion, psychosis, exfoliative dermatitis, weakness, difficulty of speech, convulsions and

* Made by Eli Lilly and Company.

collapse may occur. In my experience and that of my colleagues with the use of sulfocyanate there is definite reduction of blood pressure in more than half the cases. Certainly it is the most satisfactory drug available today for treating hypertension. Potassium sulfocyanate never should be administered for a long period unless the amount administered is based on studies of concentration of cyanates in the blood of each patient.

Rest and the reduction of nervous stresses and strains are advisable in the treatment of many patients who have essential hypertension. In general, it is advisable for patients who have hypertension to obtain nine hours of rest in bed at night, to lie down for an hour or an hour and a half in the middle of the day, to take vacations frequently, to acquire a calm, philosophic outlook on life and to avoid nervous stresses and strains. Young individuals who follow occupations that are strenuous from a nervous standpoint may well consider it advisable to change to an occupation that is more restful. Houston[20] has emphasized that hypertension responds less readily, the closer each individual patient is to the necropsy table, and has stressed the need for treatment in the early phases of hypertension or indeed before hypertension affects those who eventually will probably be afflicted with it. He wrote:

"The gravity of the threat offered by essential hypertension will justify an alteration of occupation in an attempt to seek a calmer social environment. The threat justifies our using our wits in every way we can to get a better understanding of what is meant by habit and emotional attitude in the specific case before us. The study of habit as found in John Dewey's 'Human Nature and Conduct', the study of the possibility of gaining control of the involuntary muscular action of the arteriole through a perfected control of the skeletal muscle as outlined by Jacobson in 'Progressive Relaxation' will prove helpful for understanding. It may prove helpful to realize that the 'will to power' as celebrated in success magazines and popular success psychologies constitute propaganda for emotional habits and attitudes which may in some instances be baneful, and that the doctor himself may be a therapeutic agent of great value if he can successfully propagandize and institute a different habit, the habit of equanimity, of 'Power through Repose.' (See Anna Payson Call's excellent popular book under this title.) While any emotion represents some break of smooth flow of feeling or action, emotional attitude that leads to essential hypertension

seems to be one in which a curb is placed on a strong need for action, a sense of social urgency menaced by frustration. Hard labor doesn't produce hypertension, but stress, strain, striving imply a need of action generated by social requirements but that has met with social obstacles."

Many diets have been advised for the treatment of hypertension, but there is very little evidence that diet influences blood pressure. We do not feel it advisable to restrict protein in diets of hypertensive patients who do not have renal or myocardial failure. F. M. Allen[21] originally suggested restriction of sodium chloride in essential hypertension. He found reduction of blood pressure to normal in 19 per cent of hypertensive patients who received this treatment and marked reduction of it in 42 per cent. He stressed that the salt-free diet should be secured by selection of foods which had a small content of salt and by failure to add salt in the kitchen or at the table. The salt-free diet is not looked on favorably by most students of hypertension today. I myself cannot speak authoritatively, because my experience with well-conducted studies of the method has been small. Certainly it is useless to tell a patient not to add salt to his food. If a patient is to be treated with salt restriction, he should be treated scientifically as one treats a patient with diabetes. If an adequate period of observation does not show reduction of blood pressure, this method of treatment should be abandoned.

Individuals who are overweight should reduce, for obesity throws an additional strain on the heart by increasing the work that it must do and as a result of deposition of fat in cardiac muscles and around the heart. There is some evidence also that reduction of the weight of obese people reduces blood pressure. Restriction of alcohol and coffee is not imperative unless they serve as stimulants. They do not in themselves increase the blood pressure. Indeed alcohol reduces it temporarily. Smoking greatly increases the blood pressure of many patients who have hypertension, and if this can be demonstrated by having the patient smoke after his blood pressure has reached a basal value, it is well to consider sharp restriction or complete elimination of smoking.

It is apparent that the methods of medical treatment available today are largely unsatisfactory, so far as reduction of blood pressure is concerned. That they have some value is apparent, but I believe that almost every physician who treats hypertension is dissatisfied with such therapeutic methods as are available to him today. Symptoms may be

relieved rather easily, as Ayman has pointed out. However, continued relief of symptoms may be considerably more difficult to accomplish than is temporary relief of them. Headache is the most annoying symptom of the uncomplicated stage of hypertension and there has been no satisfactory method of relieving it. It characteristically occurs in the early morning hours; it either awakens the patient or is present when the patient wakes at the usual time. It usually is described as consisting of sensations ranging from a dull ache to a severe pounding distress and it usually is located in the cervico-occipital region. Ordinarily it disappears after the patient has been active for several hours.

For many years I have been puzzled about the mechanism of hypertension headaches. The designation of them implies that they result from high blood pressure but determinations of the blood pressure of patients with hypertension hourly during rest and sleep indicate that the blood pressure decreases markedly during sleep and then when the headaches occur, the blood pressure, although elevated, is lower than it is during the periods of activity. Therefore, there must be some other explanation for hypertension headaches than the level of the blood pressure. Since the headaches occur at night during rest in the horizontal position, MacLean and I[22] felt that they might arise as a result of this horizontal position. Obviously, in order to study this condition thoroughly, patients who were having headaches almost every morning were needed in order to avoid interpreting spontaneous remissions of headaches as the result of therapy. Since our original report we have had less success in relieving hypertensive headache by having patients sleep in the "head-up" bed than we had anticipated, but the method should always be tried, and discarded if found to be without value.

My conclusion relative to failure of reduction of blood pressure by medical means is supported by the opinion of almost all those who treat patients who have high blood pressure under controlled conditions, by the high mortality caused by hypertension, and by the number of physicians who consult other physicians or refer their patients to other physicians because the physician's own medical treatment has been unsuccessful. The situation regarding the medical treatment of hypertension is roughly comparable to that regarding pernicious anemia before the discovery of the efficacy of liver extract. It may surprise younger members of the profession to know that the present-day medical treatment of hypertension is much the same as that outlined

twenty-five years ago by Elliott and that described twenty years ago by Moschcowitz with exception of the use of potassium sulfocyanate. During the intervening period several million people have died of high blood pressure in the United States. The failure to change this type of medical treatment is patently not referable to the fact that this treatment has been satisfactory but to the fact that there has been nothing better brought forth.

These observations do not release physicians from the responsibility of treating patients with hypertension. They must care for many patients with conditions for which there are no specific remedies, as for example, leukemia, chronic nephritis, lymphosarcoma, carcinoma and degenerative diseases of the nervous system. If the physician allays the patient's fears, does not subject him to inconveniencing therapeutic procedures which have no benefit, and keeps him from the hands of irregular practitioners who treat him for his monetary value, then the physician has done the patient a service. Intelligent supervision and judicious use of sedatives are helpful. If in addition the patient's blood pressure can be reduced by the use of other measures which I have discussed, the physician has added to his service to the patient.

REFERENCES

1. Hines, E. A., Jr. Range of normal blood pressure and subsequent development of hypertension; a follow-up study of 1,522 patients, *J.A.M.A.*, 1940, *115*:271.
2. Robinson, S. C. and Brucer, M. Range of normal blood pressure; statistical and clinical study of 11,383 persons, *Arch. Int. Med.*, 1939, *64*:409.
3. Goldblatt, H. Studies on experimental hypertension; the pathogenesis of experimental hypertension due to renal ischemia, *Ann. Int. Med.*, 1937, *11*:69.
4. Barker, N. W. and Walters, W. Hypertension and chronic atrophic pyelonephritis; results of nephrectomy, *J.A.M.A.*, 1940, *115*:912.
5. Hines, E. A., Jr. and Lander, H. H. Factors contributing to the development of hypertension in patients suffering from renal disease, *J.A.M.A., in press.*
6. Hines, E. A., Jr. Reaction of the blood pressure of 400 school children to a standard stimulus, *J.A.M.A.*, 1937, *108*:1249.
7. Ayman, D. An evaluation of therapeutic results in essential hypertension; the interpretation of symptomatic relief, *J.A.M.A.*, 1930, *95*:246.
8. Hines, E. A., Jr. The hereditary factor in essential hypertension, *Ann. Int. Med.*, 1937, *11*:593.
9. Keith, N. M., Wagener, H. P. and Barker, N. W. Some different types of essential hypertension: their course and prognosis, *Am.J.M.Sc.*, 1939, *197*:332.
10. Allen, E. V. and Adson, A. W. The treatment of hypertension; medical versus surgical, *Ann. Int. Med.*, 1940, *14*:288.
11. Grollman, A., Williams, J. R., Jr. and Harrison, T. R. Reduction of elevated blood pressure by administration of renal extracts, *J.A.M.A.*, 1940, *115*:1169.
12. Allen, E. V. and Hines, E. A., Jr. Fluctuations of blood pressure, *Modern*

concepts of cardiovascular disease, 1939, *8:* no.11.

13. Kapernick, J. S. *Unpublished data.*
14. Evans, W. and Loughnan, O. The drug treatment of hyperpiesia, *Brit. Heart J.*, 1939, *1:*199.
15. Barker, M. H. Symposium on nephritis: the use of cyanates in the treatment of hypertension, *Wisconsin M. J.*, 1937, *36:*28.
16. Logefeil, R. C. Observations on the use of potassium sulphocyanate (rhodan) in the treatment of essential hypertension, *Minnesota Med.*, 1929, *12:*151.
17. Barker, M. H. The blood cyanates in the treatment of hypertension, *J.A.M.A.*, 1936, *106:*762.
18. Griffith, J. Q., Jr. and Lindauer, M. A. Thiocyanate therapy in hypertension including a new micromethod for determining blood thiocyanates, *Am. Heart J.*, 1937, *14:*710.
19. Wald, M. H., Lindberg, H. A. and Barker, M. H. The toxic manifestations of the thiocyanates, *J.A.M.A.*, 1939, *112:*1120.
20. Houston, W. R. Psychic factors in essential arterial hypertension, in: *Diagnosis and treatment of cardiovascular disease* (Stroud), Philadelphia, Davis, 1940, v. *2*, p. 1497.
21. Allen, F. M. *Treatment of kidney diseases and high blood pressure.* Morristown, N. J., Psychiatric Institute, 1925.
22. Allen, E. V. and MacLæan, A. R. Vascular clinics; the relief of "hypertension" headache with the "head-up" bed; report of case, *Proc. Staff Meet., Mayo Clin.*, 1940, *15:*523.

PNEUMOCOCCAL AND "VIRUS" PNEUMONIA*

HOBART A. REIMANN

Magee Professor of Practice of Medicine and Clinical Medicine,
The Jefferson Medical College and Hospital

SO MANY excellent papers have recently been published describing clinical experiences with sulfonamide chemotherapy in pneumococcal pneumonia that it is quite needless, in the absence of any new facts, to discuss the matter at length here. Without exception, there is agreement among all observers as to the epochal nature of the discovery of chemicals which have an almost specific value in the treatment of pneumococcal infection, particularly pneumonia. There are, however, still many questions which have not yet been fully answered, five of which may be posed as follows:

1. *Is the introduction of sulfonamide therapy alone sufficient to explain the striking diminution in the death rate from pneumonia in the last few years?*

At present it is possible only to estimate the actual value of chemotherapy in pneumonia. Because of the justifiable enthusiasm attendant upon its use, there is, I believe, an understandable tendency to exaggerate the extent of the gains achieved with chemotherapy and to ignore some other factors which may also play a role. Let me cite an example to illustrate the point.

Without critical thought, a glance at a recently published chart[1] of mortality from pneumonia which shows a strikingly low death rate from pneumonia in 1938-39 as compared with 1928-29, might be taken to indicate a triumph of chemotherapy. If, however, similarly gathered statistics of other recent years are examined, the "pneumonia death rate was at a record low" in 1937-38.[2] Beginning in August 1937, every month except two showed a lower mortality rate from pneumonia than did the same month in any other year since 1920. According to another statistical report[3] by the U. S. Bureau of Census the mortality rate from "influenza and pneumonia" dropped from 207 per 100,000

* Presented October 17, 1940 in the Graduate Fortnight of The New York Academy of Medicine.

in 1900 to 114 per 100,000 in 1937. The period covered by these statistics, of course, was before chemotherapy for pneumonia was available. The increasing use of serotherapy may have played a role, but hardly enough to account for so great a reduction in mortality. Before discovering what were the important factors in lowering the death rate, it would first be necessary to know the morbidity rate of the disease. If the morbidity rate is stationary and the mortality rate reduced as much as stated there would then be reason to acclaim the success of specific therapy. Accurate figures, however, are not available. A significant fact is that in one study a drop of 27 per cent in mortality occurred in the first quarter of 1940 as compared with a like period in 1939.[4]

It is probable that numerous factors are at play. In the control of typhoid fever, for example, increased knowledge of the disease, specific vaccine, improved sanitation, improved diet, control of carriers and other measures all combined to reduce its incidence. Similar factors were operative in tuberculosis. The lowest death rates in history were also recently recorded for diarrheal diseases, appendicitis, and puerperal conditions. Whether or not serotherapy and chemotherapy are alone responsible for the recent low death rate in pneumonia, or whether its prevalence like that of other diseases is cyclical, and the present low ebb is merely a phase, only the future can tell.

Indications are also suggestive that other unknown factors may be operative. For example, in our own experience in 1939[5] with an infection of the respiratory tract, probably caused by a filtrable agent, pneumococci were surprisingly scarce. They were isolated from the sputum of only 8 out of 100 patients. It is generally believed that from 35 to 50 per cent of normal persons carry pneumococci in their nasopharynx habitually, and mild infections of the respiratory tract supposedly increase the percentage still more. The paucity of pneumococci in our own recent experience may indicate a temporary diminution in their numbers and prevalence in certain localities as a result of conditions totally unknown.

2. *Should chemotherapy be started as soon as evidence of pulmonary infection is detected?*

In this matter also, I believe enthusiasm has somewhat exceeded sound practice. On several occasions I have read printed advice recommending that chemotherapy be started as soon as a diagnosis of pneumonia is made. It would be far better, and in accord with facts, if the

recommendation were restricted to cases of clinical lobar pneumonia, or better still to cases of pneumonia caused by the pneumococcus or by the hemolytic streptococcus. Chemotherapy may also be effective in staphylococcal pneumonia. There are, on the other hand, many forms of pneumonia in which chemotherapy with the drugs available at present is of no value. Obviously every patient with fever and a few rales in the lung should not be subjected to the discomforts and hazards of chemotherapy. The sulfonamide compounds have not yet been shown to have any influence on influenza or other influenza-like pulmonary infections which have been prevalent in recent years, nor are they of value in pulmonary congestion, or in mixed infection of the lungs where bacteria susceptible to the sulfonamide compounds are not present. The important point to be made is that etiologic diagnosis should govern the type of therapy to be employed.

In recent experience I have seen a number of patients with sulfanilamide poisoning to whom the drug was given without previous attempt having been made to discover the cause of the pneumonia which was atypical in each case. In such cases, in the absence of beneficial effect after a reasonable trial of the drug, instead of stopping it, more and more is given until poisoning results. It is just as important to know when not to use chemotherapy, and when to stop it, as it is to know when to use it. It would be important to know how many patients who supposedly die from an infection, actually die from drug poisoning.

The matter of giving sulfonamide compounds to prevent the development of pneumonia has been raised. There is at present no basis for their use as prophylactics. If, for example, only 1 person out of a 1000 who has a cold develops pneumonia it is hardly justifiable to treat the other 999 with the drugs. The one person who may develop pneumonia can be treated promptly and properly after pneumonia occurs, provided it is caused by bacteria amenable to therapy. Perhaps the same reasoning may apply to the question regarding the use of sulfonamides to prevent postoperative pneumonia.

Our practice during the past winter has been as follows: When an adult patient had pneumonia which commenced in the "typical" manner, that is, suddenly with a chill, a pain in the chest, cough, rusty sputum, high fever and leukocytosis, 4 gm. of sulfathiazole was promptly given by mouth. During the next few hours, before the next dose of 1 gm. was due, the sputum was examined and the type of

pneumococcus, if present, determined. The dosage was then continued at 4 hour intervals until the temperature fell to normal and clinical recovery was evident. We have as yet had no recurrences after stopping the drug at this time.

If, however, a patient with pneumonia became ill gradually, more or less as an aggravation of a cold or influenza, without the typical symptoms and signs just mentioned, and if the leukocytes were normal or reduced in number, no sulfonamide compounds were given, unless in the examination of the sputum pneumococci of types I, II, III, V, VII, VIII or XIV or hemolytic streptococci were present in numbers sufficient to regard them as etiologically significant. Blood cultures were, of course, made routinely in all cases.

3. *When and how should serum therapy be employed?* There is much evidence available that chemotherapy is just as effective, if not somewhat more so, than specific immune serum in the treatment of pneumococcal pneumonia. This being the case, it would seem that serum is necessary only in the exceptional case. On the other hand, experimental studies show conclusively that the combination of chemotherapy and serotherapy has greater therapeutic value than either method used alone, but not enough time has elapsed to serve final judgment in the matter as regards its clinical value. Both serum therapy and chemotherapy used separately are said to reduce the mortality rate to between 3 and 10 per cent in different series of cases, and in several of them chemotherapy seems to be superior in effectiveness. Here again caution is needed in interpreting statistics. It is highly probable that while the complexity and expense of giving serum generally precludes its use for all but seriously ill patients, chemotherapy with its ease of administration and cheapness, is used much more freely and given to patients who are not seriously ill and who perhaps wouldn't be, even if untreated. Hence the recorded mortality with chemotherapy may be lower. Chemotherapy should be used alone in patients who are known to be hypersensitive to both horse and rabbit serum, when for some reason the causative pneumococcus cannot be typed or when serum cannot be obtained. Serotherapy should be employed alone in patients who are known to be sensitive to, or poisoned by, sulfonamide compounds. Combined serum and chemotherapy seems to be indicated in about 10 per cent of cases of pneumococcal lobar pneumonia.

There are a few criteria to govern whether specific antipneumococ-

cus serum should be given together with sulfathiazole. They are as follows:

a. If chemotherapy has been given for 18 to 24 hours without causing improvement.
b. In patients over 40.
c. In pregnant women or in early puerperium.
d. When more than one lobe is involved and when the blood culture is known to be positive.

4. *How do the sulfonamide compounds exert their beneficial effect in pneumococcal infections?*

At present it seems that the presence of sulfonamide compounds in some way interferes with the nutrition of bacteria so that they die off for want of food. If Lockwood's interpretation of the mechanism is correct, much depends upon the amount of nutritive peptone or other substances which is required for bacterial growth. If an abundance of nutritive material is present it may be great enough to overcome the effect of the sulfonamides and permit bacteria to thrive in spite of chemotherapy. This may be the reason why chemotherapy is of no avail in localized purulent pneumococcic disease such as arthritis or empyema, yet on this basis it is difficult to explain the striking effects of chemotherapy in some cases of pneumococcal meningitis in which pus is also present.

It is obviously a matter of great importance to discover just how the sulfonamide compounds affect pneumococci. Once this is known, it may pave the way for the development of better agents, ones which harm the bacteria more and the patient less.

5. *What is the likelihood of the future discovery or synthesis of other similar or dissimilar chemicals to cure pneumonia?*

From the rate of progress in the past few years in the chemistry of sulfonamide compounds and from the number of scientists studying the problem, there is every reason to hope for the development of even better chemicals with which to combat pneumonia. Of great interest were the studies of Avery and Dubos concerning the lytic effect of a certain enzyme on the capsular substance of type III pneumococcus. Although this enzyme is capable of curing experimentally induced pneumococcal infections in animals its use in man has not as yet been thoroughly studied. Recently an even more interesting enzyme called Gramicidin has been prepared by Dubos which serves to destroy all

gram positive bacteria. Success in using this new enzyme has already been attained in treating mastitis of hemolytic streptococcal origin in cows. Reports of the effect of this substance on pneumococcal infections are anxiously awaited.

"Virus" Pneumonia

During the past three years, especially in the winter months, an atypical form of pneumonia which could not be diagnosed on an etiologic basis was observed in Philadelphia and elsewhere. Because of its resemblance to cases of genuine influenza virus pneumonia and to the pneumonia which occurs in psittacosis and vaccinia, and because an elusive virus was isolated from a few patients, it was suggested that the term "virus pneumonia" be applied to the disease if it could be proved that a virus was the cause. Proof has thus far not been offered, hence the use of the term at present is not fully justified. Moreover, in subsequent studies I have shown that the term pneumonia only includes a few severe cases among a large number of less severe cases of the same disease in which the lungs are not involved. Therefore pending the discovery of the causative agent, I have called the disease "grip" or "an epidemic infection of the respiratory tract." It is probable that it is one of several stable or variable specific entities similar to, or related to epidemic influenza which Francis has just discussed. It is also probable that it is not a "new" disease, but a newly recognized disease which has been prevalent as long as influenza, and is separable from it only by special, recently developed methods of identification.

The disease has been described in several published papers.[5, 6] In the epidemic studied at Jefferson Hospital in 1939 about 50 per cent of the nursing staff and student body were ill. Of these, 75 per cent were ambulatory and complained chiefly of coryza, nasal obstruction, frontal headache, weakness, dizziness, sweating, and anorexia lasting for several days. Relapses were common.

About 25 per cent had to go to bed with similar but severer symptoms. All of these patients had tracheobronchitis. Actual pneumonia was detected in only 6 per cent of the whole group.

In patients with pneumonia, the onset was gradual with the symptoms and signs of the mild form of the disease, but instead of improving they became worse. Photophobia and a dry, unproductive, persistent cough developed. Profuse sweating and occasionally dyspnea and

cyanosis occurred. In most cases the lining of most of the respiratory tract seemed to be involved so that a descriptive but cumbersome name for the disease in its severest form may be nasopharyngotracheobronchopneumonia. Signs of atypical pneumonia in one or both lungs gradually appeared, and in some cases pneumonia was first discovered by roentgenography.[7] Typical signs of consolidation were seldom present.

Sputum was seldom raised and in that obtained, the usual "mouth" flora of bacteria were present. Pneumococci, surprisingly, were found in only 8 of 100 samples of sputum tested and they were of the higher numbered types. They probably had no etiological significance. The leukocytes were usually normal in number but tended to increase slightly as the disease progressed.

All patients recovered, so that no necropsy material was available for study to determine whether or not the pulmonary reaction resembled the form usually elicited by pathogenic filtrable viruses.

The treatment was symptomatic and in a few patients sulfanilamide was given experimentally with no apparent effect on the course of the disease.

Addendum

Since this paper was prepared, a number of other pertinent studies of similar or identical respiratory tract infection have been published. In two of them[8, 9] necropsy showed an unusual form of pneumonia characterized by a bacteria-free mononuclear cell infiltrate. In four other studies,[10, 11, 12, 13] published almost simultaneously, report is made of the isolation of filtrable agents from patients with infections closely resembling the ones called virus pneumonia. Studies are under way at present to determine if the "virus" pneumonia described here is etiologically related to any of these newly reported ones.

REFERENCES

1. Seasonal incidence of pneumonia greatly reduced, *Statistical Bull. Metropolitan Life Insurance Co.*, 1940, *21*, no 2: 7.
2. Pneumonia death rate at record low, *Statistical Bull. Metropolitan Life Insurance Co.*, 1938, *19*, no. 9: 6.
3. Major causes of death, increase in life expectancy, and population changes in the United States, *Pub. Health Rep.*, 1939, *54:* 2054.
4. Mortality experience of the first three months of 1940 . . . pneumonia, *Statistical Bull. Metropolitan Life Insurance Co.*, 1940, *21*, no. 4: 8.
5. Reimann, H. A. and Havens, W. P. An epidemic disease of the respiratory tract, *Arch. Int. Med.*, 1940, *65:* 138. (References)
6. Reimann, H. A. An acute infection of the respiratory tract with atypical

pneumonia, *J.A.M.A.*, 1938, *111:* 2377.

7. Kornblum, K. and Reimann, H. A. The roentgenological aspects of an epidemic of acute respiratory infection, *Am. J. Roentgenol.*, 1940, *44:* 333.
8. Kneeland, Y. and Smetana, H. F. Current bronchopneumonia of unusual character and undetermined origin, *Bull. Johns Hopkins Hosp.*, 1940, *67:* 229.
9. Longcope, W. T. Bronchopneumonia of unknown etiology (Variety X), *Bull. Johns Hopkins Hosp.*, 1940, *67:* 268.
10. Magill, T. P. A virus from cases of influenza-like upper respiratory infection, *Proc. Soc. Exper. Biol. & Med.*, 1940, *45:* 162.
11. Dyer, R. E., Topping, N. H. and Bengtson, I. A. An institutional outbreak of pneumonitis; isolations and identification of causative agent, *Pub. Health Rep.*, 1940, *55:* 1945.
12. Francis, T. A new type of virus from epidemic influenza, *Science*, 1940, *92:* 405.
13. Weir, J. M. and Horsfall, F. L., Jr. The recovery from patients with acute pneumonitis of a virus causing pneumonia in the mongoose. *J. Exper. Med.*, 1940, *72:* 595.

NEWER KNOWLEDGE OF THE VITAMIN B-COMPLEX*

NORMAN JOLLIFFE

Associate Professor of Medicine, New York University, College of Medicine

Our newer knowledge of nutrition has resulted mainly from clinical studies made possible by the isolation and synthesis of many of the vitamins by the biochemists. In 1920 none of the vitamins then known, vitamins A, B_1, B_2, C and D, had been chemically identified or synthesized. By 1940, all of the vitamins distinguished alphabetically in 1920 have been identified chemically and synthesized. In addition, vitamins E, K, P, and ten or more additional B-vitamins have been discovered. Of these, alphatocophorol, several naphthoquinones, nicotinic acid, pyridoxin, and pantothenic acid have been synthesized. These discoveries of the biochemists, if applied to the prevention and treatment of human disease, may be compared, in importance, to the discoveries in bacteriology made in the decades on either side of 1900.

Application by clinical investigators of the biochemical discoveries made in the group of B-vitamins has been so rapid that in this review the title "Newer Knowledge" will be arbitrarily defined as including only 1939 and 1940.

The vitamin B-complex is now known to contain at least a dozen fractions, five of which are available in crystalline form in amounts adequate for clinical use. These are thiamin hydrochloride (B_1), riboflavin (B_2), nicotinic acid (p-p factor), pyridoxin (B_6) and pantothenic acid (filtrate factor). Through the controlled use of these crystalline B-vitamins, clinical investigators have made, in the past two years, progress far beyond what was possible when only concentrates were available. This progress may be summarized broadly as follows:

1. Additions to our knowledge of the clinical manifestations of a deficiency in the B-vitamins.

* Given November 7, 1940 at the Stated Meeting of The New York Academy of Medicine.
From the Department of Medicine, New York University, College of Medicine and the Medical Service of the Psychiatric Division, Bellevue Hospital, New York.

2. Additions to the list of diseases known to be due to nutritional deficiency.

3. The increasing recognition that deficiency disease in man is usually not single but multiple.

4. The development of laboratory methods to aid in the diagnosis of deficiency diseases.

5. The recognition of the necessity for restoration to staple foods of vitamins removed in processing.

Thiamin Hydrochloride

Our newer knowledge of thiamin hydrochloride consists in additions to the list of its deficiency manifestations, and in the development of laboratory methods for its quantitative determination in blood and urine. As application of these methods to the diagnosis of thiamin deficiency is still in the early experimental stage, they will not be treated in detail.

In February 1939, before this audience, I[1] divided the clinical manifestations into (1) anorexia and fatigue, (2) a neurologic syndrome, and (3) a circulatory syndrome. At the present time the neurasthenic syndrome replaces anorexia and fatigue, and part of Wernicke's syndrome is added to the neurologic manifestations. No significant additions have been made to our knowledge of the circulatory syndrome.

The neurasthenic syndrome is probably the most common manifestation of isolated vitamin B_1 deficiency. As in neurasthenic syndromes of any origin, the symptomatology is varied but its outstanding characteristics are anorexia, fatigue and insomnia. Completing the picture of neurasthenia are such complaints as irritability, "gas," nausea, constipation, uncomfortable sensations in the abdomen and other parts of the body, depression, backache, headache (usually of the occipital or constricting band type), sighing, palpitation, and precordial distress. For several years I have been cognizant of this group of symptoms in patients having the objective signs of vitamin B_1 deficiency. I usually attributed this group of symptoms to neurasthenia on the basis of an abnormal psyche which led to further dietary restrictions and, in turn, to the development of objective signs. I still believe this to be true of certain patients. Adequate treatment for the deficiency was followed not only by disappearance of the objective signs but also, again in certain instances, of the neurasthenic syndrome. I then applied, to sub-

jects having the neurasthenic syndrome without objective signs of vitamin deficiency, the treatment-regimen of dietary correction, vitamin supplements rich in the entire B-complex, and thiamin hydrochloride. Many of these patients, though not all, were helped. The improvement was attributed to better nutrition plus the psychotherapy of this dietary regimen. Not until Williams, Mason, Wilder and Smith,[2] in a well-controlled experiment with human subjects, reproduced this characteristic neurasthenic syndrome by inducing an isolated thiamin deficiency, have I been willing to include it as a manifestation of vitamin B_1 deficiency. It should not be inferred, however, that all neurasthenia is based on thiamin deficiency. Such is definitely not the case. Almost any agent causing the triad of anorexia, fatigue, and insomnia, if not soon relieved, will cause, in susceptible persons, the development of other neurasthenic symptoms. Nevertheless, the proportion of neurasthenia caused by vitamin deficiency may be larger than is now commonly believed.

Williams, Mason, Wilder and Smith, in their subjects in whom isolated thiamin deficiency was experimentally produced, noted the regular development of electrocardiographic abnormalities. "They consisted of diminution in the amplitude of all complexes and particularly of the T waves of the chest leads. In certain instances the T waves became isoelectric or shallowly inverted. On restitution of thiamin to the diet the electrocardiograms became normal." These observations of the Mayo group confirm the findings of Jolliffe, Goodhart, Gennis and Cline,[3] in whose experimental subjects precordial pain and electrocardiographic abnormalities were likewise observed. It may be that in persons past middle age the coronary arteries have at times been unjustly condemned on the history of precordial pain plus abnormalities in the electrocardiogram.

The central neurologic manifestations of thiamin deficiency occur only after peripheral polyneuropathy is evident, and form a part of Wernicke's syndrome. As demonstrated by Jolliffe, Wortis and Fein,[4] the oculomotor palsies of this syndrome are a vitamin B_1 deficiency manifestation and respond to adequate dosage of thiamin hydrochloride. On occasion the stupor will respond to similar therapy, but the ataxia shows no such response. The syndrome as originally described by Wernicke is a multiple deficiency, and the clinical picture seen is dependent upon the multiplicity of factors involved.

Riboflavin

Our clinical knowledge of riboflavin deficiency dates back only to December 1938 when the preliminary note of Sebrell and Butler[5] appeared.

The lesions produced by Sebrell and Butler in women maintained with the diet of Goldberger and Tanner appeared 94 to 130 days after the beginning of the experiment. They began "as a pallor of the mucosa of the lip in the angles of the mouth without involvement of the buccal mucosa. This pallor was soon followed by maceration, and within a few days superficial transverse fissures appeared, usually bilateral, and exactly in the angle of the mouth. In some instances the fissures continued onto the skin for a distance of as much as half an inch. These lesions resemble those described as perlèche. At about the time the fissures were seen, the lips became abnormally red along the line of closure. This was due, apparently, to a superficial denudation of the mucosa. In addition to the cheilosis, there was also seen a fine, scaly, slightly greasy desquamation on a mildly erythematous base in the nasolabial folds, on the *alae nasi*, in the vestibule of the nose and on the ears." Kruse, Sydenstricker, Sebrell and Cleckley[6] have reported, in addition, a keratitis associated with these signs of riboflavin deficiency.

Jolliffe, Fein and Rosenblum[7] have reported fifteen subjects having lesions due, we believe, to riboflavin deficiency. Thirteen of these subjects were alcoholic, one had advanced pulmonary and intestinal tuberculosis, and one was an epileptic. In this group of fifteen patients thirteen also had nicotinic acid deficiency; seven, vitamin B_1 deficiency; and three, vitamin C deficiency; while only one showed no clinical evidence of another vitamin deficiency. Since then, however, we have observed many subjects having a cheilosis which responded to treatment with synthetic riboflavin, who presented no clinical evidence of another deficiency disease. The facial lesions seen in the fifteen cases reported consisted of filiform excrescences of a seborrheic nature, apparently derived from the sebaceous glands, varying in length up to 1 mm., closely to sparsely scattered over the skin of the face. Their characteristic location was in the nasolabial folds, but in addition they occurred frequently on the *alae nasi*, occasionally on the bridge of the nose, and sometimes on the forehead above the eyebrows. The skin on which the excrescenses were located was the seat of a fine, scaly, greasy desquamation. On

casual inspection these filiform lesions resembled urea frost, but they could not be brushed off by rubbing with the fingers. In addition, most of the patients showed fissures and maceration at the angles of the mouth, and a degenerative crustlike formation on the epithelium of the lips, most marked on the lower. The fissures at the angles of the mouth were bilateral and extended laterally 1 to 3 mm. onto the mucous membrane of the mouth and 1 to 10 mm. onto the skin. They were usually very shallow but sometimes were 0.5 mm. deep, and their bases as a rule showed little or no increased redness. Extending for 5 to 20 mm. from the angle of the mouth onto both lips, the mucous membrane was macerated and wrinkled and pearl-gray. The lips, particularly the lower, frequently showed a marked increase in the vertical fissuring, often without a break in the mucous membrane. Occasionally the vestibule of the nose was involved with lesions similar to those on the lips.

By maintaining patients having these characteristic lesions of riboflavin deficiency with a control diet poor in the B-complex, we demonstrated that these lesions respond to the administration of synthetic riboflavin, but not to thiamin hydrochloride, or nicotinic acid.

Nicotinic Acid

The signs and symptoms of partial chronic nicotinic acid deficiency, particularly those occurring in pellagrins, are so well known that it is not necessary to describe them in detail. The complete picture consisting of a scarlet-red stomatitis and glossitis, diarrhea, bilateral symmetrical dermatitis, and mental aberrations, forms in combination such a characteristic syndrome that it is widely known and should never go unrecognized. It is not so well understood, however, that the oral lesions, the gastrointestinal lesions, the mental changes or the skin lesions may each occur alone or in any possible combination. For example, patients having the stomatitis of nicotinic acid deficiency are too frequently considered to have only the superimposed Vincent's infection. The primary diagnosis is not considered and specific therapy is neglected. If nicotinic acid therapy is instituted, not only is the scarlet-red stomatitis blanched within 24 to 48 hours, but the Vincent's infection heals without other general or local therapy. Then mental changes may precede the skin, gastrointestinal or oral changes, and the patients may be labeled as neurasthenic, neurotic or psychoneurotic. Similarly, gastrointestinal manifestations may precede all the others, and the diagnosis

may be missed for many weeks.

Jolliffe, Bowman, Rosenblum and Fein[8] have reported 150 cases of an "encephalopathic syndrome," a condition heretofore almost always fatal, which is caused, it is believed, by nicotinic acid deficiency. This syndrome may occur as the only clinical manifestation of a deficiency disease or it may occur in association with pellagra, polyneuropathy due to vitamin B_1 deficiency, the oculomotor disturbances of Wernicke's syndrome or scurvy. The clinical picture of this encephalopathic syndrome is more or less well-defined and is characterized by clouding of consciousness, cogwheel rigidities of the extremities, and uncontrollable grasping and sucking reflexes. The vigorous use of nicotinic acid has reduced the mortality in this syndrome from almost 100 per cent to about 15 per cent.

Pyridoxin

A syndrome in man attributable to a deficiency of vitamin B_6 or pyridoxin has not as yet been reported as a distinct clinical entity. In rats, a deficiency of this vitamin is known to cause "rat acrodynia," foci of degeneration in striated and cardiac muscle, and changes in the nervous system, particularly of the columns of the spinal cord. Antopol and Schotland[9] have recently suggested that vitamin B_6 through its pyridine structure may be involved in the enzyme system concerned in muscle metabolism. In this connection it is interesting to note that Spies, Bean and Ashe[10] have described a syndrome characterized by "extreme nervousness, insomnia, irritability, abdominal pain and difficulty in walking," which disappeared dramatically following the intravenous administration of pyridoxin, but which could not be relieved with nicotinic acid, thiamin hydrochloride or riboflavin. This syndrome, however, has not as yet been observed by others. Antopol and Schotland[9] have reported the beneficial effect of pyridoxin on muscle strength in six patients having pseudohypertrophic muscular dystrophy, but warned that "it is not to be implied that this group of muscular dystrophies are due to avitaminosis B_6." In addition, we have accumulated evidence that vitamin B_6 plays some part in the adolescent acne syndrome.

Syndromes collectively labeled paralysis agitans, while not directly fatal, usually follow a progressive course, the victims eventually becoming helpless and seeking hospitalization. Since muscular rigidity and

weakness is characteristic of paralysis agitans, and since vitamin B_6 is involved in muscle metabolism, it seemed worth while to test its effect in this syndrome. I therefore selected fifteen patients having paralysis agitans, all of whom were bedfast or chairfast, ten for more than three years, and administered to each 50 or 100 mg. of vitamin B_6 hydrochloride by intravenous injection, either daily or every other day. Of the fifteen patients, four showed subjective and definite objective improvement. Two additional patients were subjectively improved. These results were reported on April 24, 1940 before the Minnesota State Medical Association.[11] Similar results were later reported by Spies, Hightower and Hubbard.[12] Since then I have treated forty ambulant patients having the paralysis agitans syndrome with pyridoxin. Approximately 20 per cent showed definite objective improvement of dramatic proportions. Improvement in some degree was noted, however, in about two-thirds of the patients. It appears, therefore, that the syndrome of paralysis agitans includes a group of persons whose symptoms, particularly the rigidities and weakness, respond to pyridoxin.

Restoration to Flour of Vitamins and Minerals Removed in Processing

It is not surprising that coincidentally with our newer knowledge of nutrition, the necessity for restoring to staple foods the vitamins and minerals removed in processing should receive increasing attention. "England," to quote from a recent editorial in the Journal of the American Medical Association,[13] "locked in the struggle of total war and conscious of the importance of maintaining at high levels the strength and courage of its people, has fortified margarine with vitamin A and restored calcium and thiamin hydrochloride (vitamin B_1) to flour." In our country, surveys made by Stiebeling and Phipard[14] show the diets of wage earners and clerical workers to contain inadequate or borderline amounts of several vitamins and minerals. The more serious inadequacies were in the B-vitamins, in iron and in calcium. Sebrell[15] has pointed out "that in all probability the nutritional diseases constitute our greatest medical and public health problem, not from the point of view of deaths, but from . . . disability and economic loss." Even the best fed members of our population today consume less vitamin B_1 than did the parish poor of 100 years ago.[16] How has this situation come about here in America?

At the present time the American dietary contains about 650 calories derived from white flour (daily per capita consumption equals 6.5 ounces), practically vitamin- and iron-free, and an equal number of vitamin-free calories from sugar (daily per capita consumption equals 5.5 ounces). In combination, these sources account for 50 per cent of our daily average consumption of 2500 calories. They provide about 50 I.U. of vitamin B_1. In 1840 this same number of calories, derived chiefly from stone ground flour, with sugar accounting for but 25 calories per day, provided a minimum of 600 I.U. of vitamin B_1, and about a proportional increase in the other B-vitamins. Since 1840 the progressively diminishing consumption of wheat flour, combined with the removal of most of the vitamin and mineral content of the wheat berry by high milling and with the marked increase in sugar consumption has produced reduction by two-thirds of the vitamin B consumption of the American people, bringing it down to levels definitely dangerous from a public health standpoint.

Following the principle that flour should be restored to the vitamin and mineral levels of the flour of 85 per cent extraction, in use a century ago, each pound would have to contain about 1.66 mg. of thiamin hydrochloride, 1.2 mg. of riboflavin, 10 mg. of nicotinic acid, 20 mg. of iron, and 175 mg. of calcium.

Another principle to follow in restoration of flour is to restore in the average amount consumed daily (6.5 ounces) approximately one-fourth of the satisfactory daily requirement of any vitamin or mineral for which flour is a good carrier. To restore flour to this level, each pound would have to contain about 1.66 mg. of thiamin hydrochloride, 1.22 mg. of riboflavin, 6.15 mg. of nicotinic acid, 100 U.S.P. units of vitamin D, 6.15 mg. of iron, and 500 mg. of calcium. It is perhaps equally important to set maximum limits on the quantities of these vitamins and minerals added to flour, for there may be certain commercial advantages in claiming a higher vitamin or mineral content. In addition, it is probably in the interest of the consumer that flour should carry only its own burden, and not be fortified to provide for the vitamin and mineral deficiencies of sugar. Each industry should carry its own burden. A satisfactory overage would be 50 per cent in the case of thiamin, riboflavin, nicotinic acid and vitamin D. For iron, the maximum should be about 20. mg. per pound to allow for the high iron content of whole wheat; for calcium, as high as 2.0 grams per pound should be permitted

in order to allow for the calcium additions to certain self-rising flours.

Whichever principle is adopted as a basis for restoring flour to a satisfactory nutritional level, it may be accomplished by three possible methods:

1. By retaining these substances in the flour. This could be accomplished by milling to only 85 per cent extraction. Bread from such flour would be dark brown, and unacceptable esthetically, gustfully and intestinally to a great number of people. Nutritionally this method seems preferable, but I doubt whether extensive public health education and publicity could make dark bread acceptable to a majority of the American people.

2. By restoring to patent flour the required amounts of vitamin and minerals. These substances could be added either by the miller or baker. Bread from such flour would be white and its baking qualities unchanged. The cost would be about 75 cents per barrel of flour, or one-fourth cent per pound-loaf of bread.

3. By a combination of methods. Patented processes have already been devised for retaining in patent flour certain streams of the mill, rich in some of these vitamins and minerals, which hitherto had been excluded. Partial or absolute deficits can then be made up by adding the required substances. Bread from these flours has a slightly creamy color and a "wheaty" taste. Another combination method would be to substitute high B_1 baker's yeast for ordinary baker's yeast, and make up the deficit in the other nutritional factors by adding the required substances. It may be that in future a baker's yeast will be grown that will contain, in addition to unusual amounts of thiamin, the requisite balance of nicotinic acid and riboflavin, leaving only vitamin D and the minerals to be added to the flour.

Whatever method is employed, the restoration of these vital food elements to flour would result in improved nutrition for the entire population.

REFERENCES

1. Jolliffe, N. The diagnosis, treatment, and prevention of vitamin B_1 deficiency, *Bull. New York Acad. Med.*, 1939, *15:* 469.
2. Williams, R. D., Mason, H. L., Wilder, R. M. and Smith, B. F. Observations on induced thiamine (vitamin B_1) deficiency in man, *Arch. Int. Med.*, 1940, *66:*785.
3. Jolliffe, N., Goodhart, R., Gennis, J. and Cline, J. K. The experimental production of vitamin B_1 deficiency in normal subjects, *Am. J. M. Sc.*, 1939, *198:* 198.

4. Jolliffe, N., Wortis, H. and Fein, H. D. Wernicke's syndrome. *Unpublished.*
5. Sebrell, W. H. and Butler, R. E. Riboflavin deficiency in man; preliminary note, *Pub. Health Rep.*, 1938, *53:*2282.
6. Kruse, H. D., Sydenstricker, V. P., Sebrell, W. H. and Cleckley, H. M. Ocular manifestations of ariboflavinosis, *Pub. Health Rep.*, 1940, *55:* 157.
7. Jolliffe, N., Fein, H. D. and Rosenblum, L. A. Riboflavin deficiency in man, *New England J., Med.*, 1939, *221:*921.
8. Jolliffe, N., Bowman, K. M., Rosenblum, L. A. and Fein, H. D. Nicotinic acid deficiency encephalopathy, *J. A. M. A.*, 1940, *114:*307.
9. Antopol, W. and Schotland, C. E. The use of vitamin B_6 in pseudohypertrophic muscular dystrophy, *J. A. M. A.*, 1940, *114:*1058.
10. Spies, T. D., Bean, W. B. and Ashe, W. F. A note on the use of vitamin B_6 in human nutrition, *J. A. M. A.*, 1939, *112:* 2414.
11. Jolliffe, N. Clinical aspects of vitamin B deficiencies, *Minnesota Med.*, 1940, *23:* 542.
12. Spies, T. D., Hightower, D. P. and Hubbard, L. H. Some recent advances in vitamin therapy, *J. A. M. A.*, 1940, *115:*292.
13. Editorial. Vitamins for war, *J. A. M. A.*, 1940, *115:*1198.
14. Stiebeling, H. K. and Phipard, E. F. *Diets of families of employed wage earners and clerical workers in cities.* U. S. Dep't. Agriculture, Circular 507, 1939.
15. Sebrell, W. H. Nutritional disease in the United States, *J. A. M. A.*, 1940, *115:*851.
16. Jolliffe, N. A clinical evaluation of the adequacy of vitamin B_1 in the American diet, *Internat. Clin.*, 1938, *4:*46.

OSTEOMYELITIS AND PYOGENIC INFECTIONS OF JOINTS*

MATHER CLEVELAND

Orthopedic Surgeon, St. Luke's Hospital

THE English translation of Ambrose Paré's surgery, Book 19, Chapter 26, published in London in 1634, is titled, "Why Bones Become Rotten and By What Signs It May Be Perceived." Nearly 250 years elapsed before Pasteur's experiments established bacteriology and afforded the possibility of studying the infections in such a way that tuberculosis, syphilis and pyogenic infections could with certainty be recognized and classified as such. Taking Paré's text, "why bones become rotten," it is the purpose of this study of pyogenic suppurative disease of bones and joints to present a few phases of the problem as they exist today.

I am informed that an actuary considers that any attempt to draw conclusions on less than 10,000 samples is worthless. This should, if it be strictly true, make it extremely difficult for any single physician or group of physicians to speak dogmatically about any given medical subject. While most medical literature deals with a relatively small number of patients, perhaps by adding the experience of many physicians and pegging a few facts where there is agreement of opinion, a measure of truth may be gleaned.

In preparing this resume I have drawn from our clinical material on the orthopedic service at St. Luke's Hospital and I have consulted a number of surgeons who have recently written on the subject. I wish to acknowledge Wilensky's monograph,[1] the writings of Beekman and Sullivan,[2] Kennedy,[3] Phemister[4] and Starr.[5] I have, fortunately, been able to secure unpublished communications from J. Albert Key,[6] John Wilson[7] and Edwin Ryerson[8] which formed part of a symposium on osteomyelitis presented at the meeting of the American Orthopaedic Association of 1939.

Osteomyelitis or arthritis resulting by direct extension from the overlying skin as seen in compound fractures and gunshot wounds may

* Read October 16, 1940 in the Graduate Fortnight of The New York Academy of Medicine.

produce serious disability. The problem of properly immobilizing fractures that have to be transported in order to prevent simple fractures from being compounded cannot be overemphasized. If the compound fracture is present, a prompt debridement of the wound and definite, effective immobilization of the fracture until union takes place should prevent or materially lessen the incidence of this type of bone and joint infection. Should infection occur, adequate drainage must be provided, maintaining immobilization. Our experience at St. Luke's Hospital on the orthopedic service with these infected compound fractures and gunshot wounds has been of a salvage nature. In no instance has the original treatment been under our supervision and it therefore seems advisable to omit their consideration.

In osteomyelitis due to extension from an adjacent soft tissue abscess it may be conceded that earlier and more adequate drainage would greatly diminish the chance of extension to nearby bone. Of this type of osteomyelitis we have had none to treat as our colleagues in surgery and otolaryngology treat the infected fingers and middle ears respectively.

Hematogenous acute osteomyelitis or arthritis is a blood stream infection with a portal of entry or primary focus which in many instances cannot be recognized. Cuts, abrasions, infected blisters and furuncles afford such a portal from the skin to the blood stream, while diseased tonsils or pharynx or even typhoid ulcers of the intestinal mucosa represent various portals from the mucous membranes. This disease occurs predominately in the first two decades of life, and boys are more frequently subject than are girls.

Considering this disease as an acute blood stream infection or bacteremia, the localization in any given bone or joint is only an unfortunate event in its course. The fact that such localization often presents the first tangible evidence of the disease and that it affords a point of surgical attack has led to a cart-before-the-horse method of reasoning in the treatment of this at times terrifying clinical picture.

The minute anatomy of the long bones, which has been carefully studied, affords ample reason for the localization of bacterial emboli at certain recognized sites. The nutrient artery breaks up into terminal arterioles in the metaphysis adjacent to the epiphyseal line and here the infected emboli lodge. There is said to be no phagocytic action in the bone marrow. A vascular thrombosis occurs with death of tissue depend-

ing upon the extent of the thrombosis. This death of bone tissue varies from microscopic to massive bone slough or sequestration. Since bone is a rigid tissue, the formation of slough and repair by new bone or involucrum takes many months in contrast to abscess in soft tissue. The suppuration which attends this infected thrombosis spreads through the cortex of the bone, beneath the periosteum to the soft tissues. In the case of the upper femoral metaphysis, which is wholly within the capsule of the hip joint, such a spread of suppuration invariably results in a suppurative arthritis. Similar suppurative infections of bones adjacent to joints may, if undrained, invade the knee, ankle, shoulder or wrist joints, etc. A suppurative arthritis per se with no preëxisting bone involvement occurs at times, due most frequently to gonococcus and less frequently to streptococcus and pneumococcus.

Since the bones most frequently involved in this disease are the long bones of the lower extremity, the pelvis and the vertebrae, i.e., those involved in weight-bearing, the question arises whether trauma may not play some role in the localization.

When one considers the fact that the vast majority of known primary foci in this disease arise on the skin, it is not surprising that staphylococcus of various types is the predominating bacterial agent responsible for this infection. On this point, there is universal agreement. It has been stated that as high as 90 per cent of these infections occurring between the ages of two and twenty years are due to staphylococcus. Streptococcus is second in frequency, and in patients under two years of age the frequency of streptococcus infection is high. After streptococcus there follow pneumococcus and Bacillus typhosus in that order as causative organisms.

The clinical picture that these patients with hematogenous acute osteomyelitis present is primarily one of sepsis. The primary focus may be lost sight of, or forgotten. The patient is seen with chills, fever, at times between 105 and 106 degrees, leukocytosis up to 80,000 and often profound toxemia. If there is localization there will be severe pain at or near the epiphyseal line of a long bone, limited motion and spasm in the adjacent joint, some swelling due to edema and exquisite tenderness. If such a patient is seen within five to eight days of the onset of illness, the roentgenogram will show little or nothing that is of diagnostic help. In certain fulminating cases death may supervene before any localization in bone takes place.

In differential diagnosis, several diseases must be ruled out. Gonococcus arthritis in a fulminating form may be confusing, but there is usually a history of multiple joint pains before the one joint becomes swollen, red, hot and painful. Aspiration of the joint and culture of the purulent fluid will establish the diagnosis. In scurvy the roentgenogram should show subperiosteal hemorrhage.

Acute rheumatic fever presents a hurdle over which, I must confess, I have tripped on one occasion. This embarrassing situation has been summed up by one surgeon who states that, "When acute rheumatic fever presents an abscess, it's osteomyelitis."

If the patient survives the initial onslaught of the disease and shows localization in a bone or joint, the question of treatment arises, and here there is difference of opinion. Divergence of thought among physicians who are intelligently and carefully studying the same subject with a full understanding that each is talking about the same condition may be extremely helpful. However, it is futile to present a jumble of infected compound fractures, hematogenous acute osteomyelitis and protracted cases of bone infection. Conclusions drawn from such diverse conditions can be of little value.

There is honest and reasonable difference of opinion regarding the proper procedure in the treatment of hematogenous acute osteomyelitis. However, the divergence is not as wide as might be expected. The disease in its onset is admittedly a general blood stream infection, and the treatment must be supportive. Dehydration, toxemia and exhaustion must all be combatted in many instances. Blood cultures should be taken at once and repeated at definite intervals. Many observers lay great stress on the bacterial concentration in the blood as a prognostic aid. A negative blood culture may only signify that at that particular moment there were no bacteria in the blood stream or it may mean that the blood stream infection has burned itself out and has been overcome. When there are consistently but few colonies of bacteria per cc. of blood, the prognosis is good; while a persisting large number of bacterial colonies per cc. means a grave prognosis. Staphylococcus bacteremia is more serious than that due to streptococcus. The incidence of positive blood culture varies considerably as may be seen in a series of three reports comprising 184 cases. In each instance a blood culture was taken. One series reported an incidence of 34 per cent positive blood cultures and another 67 per cent positive cultures. The average

for the entire 184 cases was 56.5 per cent positive. The incidence of positive blood culture is doubtless influenced by the time after onset of the disease that the culture is taken.

During this period of investigation and supportive treatment, the importance of repeated blood transfusions cannot be overemphasized. Up to this point most competent observers are in agreement. When there is definite localization in bone or joint, opinion varies as to the next step. There are those who claim that any surgery is futile and meddlesome, and even jeopardizes the patient's chance of recovery. Some of these surgeons insist on letting nature evacuate an abscess and others will incise and drain when there is frank pus. On the other hand, a larger group of surgeons believe that after properly fortifying the patient, any recognizable localized suppuration of bone or joint should be drained with minimal trauma and little or no insult to bone or soft tissue. The day of early radical surgery on these patients has gone, leaving a great many needless cripples to haunt our clinics and hospitals as reminders of an era of doubtful judgment when scalpel, mallet and chisel ruled the scene. All surgeons now agree that absolute rest and protection of the infected bone or joint must be secured by plaster-of-Paris bandage or brace.

To date the specific treatment of these infections has been largely unsuccessful. Those few which are due to hemolytic streptococcus have been influenced by sulfanilamide and allied drugs, but the vast majority which are due to staphylococcus have not been helped. I can find no agreement that bacteriophage is helpful in those cases nor that vaccines or sera have any influence.

The mortality in these cases occurs chiefly in the first week or ten days after onset in those patients in the first two decades of life. Since the proven presence of bacteria in the blood stream indicates that the general infection predominates, a higher mortality should be expected among those patients who show this evidence of sepsis. When death occurs, it is due to sepsis and to metastatic spread to soft tissues, pericardium, endocardium, meninges. The reported mortality varies almost unbelievably from 1.5 per cent to 26 per cent. This is probably due in part to the fact that authors are not reporting strictly the same condition. Some will adhere rigidly to hematogenous acute osteomyelitis, while others may include haphazardly cases of infected compound fractures, extension osteomyelitis and bone infections that have been seen

years after onset of the disease. In two recently reported series of cases, strictly limited to hematogenous acute osteomyelitis, the mortality was 9 per cent in 33 cases and 17.5 per cent in 218 cases respectively. It is agreed that it is a serious disease with a relatively high mortality.

When these patients are seen early and carefully and skillfully treated, early healing of the local bone condition may ensue in as high as 50 per cent of the cases. Twenty-five to 35 per cent or more will show sequestration, delayed healing and additional foci in bones and joints. Fifteen to 25 per cent of these cases may be fatal.

Those patients who heal early and remain healed and those unfortunates who succumb, no longer remain a surgical problem, but that intermediate group which presents the phenomena of delayed healing, additional foci, growth disturbances, deformities of bones and joints, contribute to that vast army of chronic suppurative bone and joint infection which haunts our hospitals and outpatient departments. One cannot escape the feeling that much of this is due to ill-advised original surgical treatment, where superimposed on vascular and infectious trauma is the insult of improperly placed incisions, too wide removal of uninvolved bone and failure to immobilize the damaged part.

Here the problem of wound healing is paramount, and various methods of sterilization of the sinuses have been advocated. Almost every known chemical has been tried. Maggots have been depicted as chewing up dead bone while it seems quite likely that their urinary secretions are the only factor of value. Such demonstrations of this method of treatment as I have seen have made me feel the urge to reach for a flit gun.

At the present time in most capable hands the most universally approved treatment of this chronic suppurative infection of bone is debridement, removal of obvious sequestra, a pack of vaseline gauze and application of a plaster-of-Paris bandage for immobilization.

The orthopedic service of St. Luke's Hospital has treated during the past 10 years 56 cases of hematogenous acute osteomyelitis, a mere drop in the statistical bucket. From these patients we have learned a great deal and a debt of gratitude is herewith acknowledged. Thirty-four of these 56 patients came to us during the acute stage of their disease, while the remaining 22 consulted us for recurrence of their original disease, for metastatic foci or for the correction of deformities incident to their original lesions.

Age At Onset. The disease is definitely and predominately one of

the first two decades of life. Eighty-seven per cent of our patients were under 20 years of age at the time of onset of their disease. The age incidence is as follows:

1 year and under	6	87.5 per cent		21-30 years	2
1-2 years	1			31-40 "	1
2-10 "	24			41-50 "	3
11-20 "	18			51-60 "	1

Total 56

There were 33 males and 23 females among these patients.

THE BONES OR JOINTS INVADED WERE AS FOLLOWS

Weight-bearing Bones or Joints		Non-weight-bearing Bones or Joints	
Femur—Upper metaphysis and hip joint	16	Humerus	5
Lower metaphysis	17	Shoulder joint with no bone involved	2
Tibia — Upper metaphysis	6	Scapula	1
Lower metaphysis	6	Clavicle	1
Entire shaft	2	Radius	1
Pelvis	2	Ulna	1
Spine	3	Elbow joint	1
Sacroiliac joint	3		—
Os calcis	3	Total	12
Fibula	2		
Ankle and tarsal joints 1 each	2		
Phalanx of foot	1		
Rib	1		
Hip joint without bone involvement	4		
Knee joint without bone involvement	2		
	—		
Total	70		

Among these 82 lesions there were only 8 instances in 5 patients in which a joint was primarily invaded without bone involvement. These patients except 1 were under 2 years of age, and the causative organism was proved to be streptococcus in each of the 4 patients whose bacteriological study is recorded.

Bacteriology. In 34 of the 56 patients the bacterium responsible

for the disease is known. Every patient with hematogenous acute osteomyelitis must at some time have had a positive blood culture. In 26 of our patients in the acute stage of the disease a blood culture was taken and found to be positive in 19, an incidence of 73 per cent. Among these positive blood cultures there were 15 due to staphylococcus and 4 due to streptococcus, an incidence of almost 4 to 1 in favor of staphylococcus.

Cultures from the purulent exudate from the wounds revealed staphylococcus 21 times, streptococcus 3 times and a combination of staphylococcus and streptococcus 3 times.

Staphylococcus was the responsible organism in 79 per cent of the cases by blood culture and in 77 per cent by culture of the purulent exudate.

Each of these 2 bacteria has shown a selective action in this small series. Staphylococcus attacks the bones primarily, and we have no proved case of infection by this organism under the age of 2 years. Streptococcus tends primarily to invade the joints without bone involvement. It was the only known organism responsible in 3 out of 4 instances occurring under 2 years of age.

Treatment. Surgery on these patients presents numerous problems which must be confronted carefully and patiently. Thirty-nine, or approximately 70 per cent, of these 56 patients had a single focus of bone or joint infection, while 11 had 2 foci, 4 had 3 foci, 1 had 4 foci and 1 had 5 foci.

Forty-eight patients either in the acute or protracted stage of the disease required incision and drainage, and of these, 9 patients seen in the acute stage healed rapidly and have remained well with one operation only. The other 39 patients treated with drainage have had multiple operations, many performed in other hospitals, an average of approximately 3.5 per patient.

There were 8 patients who came to us with deformities incident to the ravages of the disease who were subjected to reconstructive operations. With but few exceptions all these patients had a prolonged hospital stay.

Complications

Ankylosis of Joints. Hip joint. There were 16 instances in which the upper extremity of the femur was invaded with the hip joint sec-

ondarily involved in each, and 4 instances of primary suppurative infection of the hip joint. The end result is known in 19 of these 20 patients and in no instance did the hip joint escape major damage.

Of the 16 patients with primary involvement of the upper femoral metaphysis and secondary suppurative arthritis of the hip, the end result is known in 15. In 11 patients, spontaneous fusion of the joint resulted, 2 were surgically fused and 2 others need surgical fusion. In each instance among those cases in which it was possible to recover bacteria from the blood stream or purulent exudate, staphylococcus was found. There is no instance in this series in which a staphylococcus infection of the hip joint failed to destroy that joint.

Of the 4 patients with primary suppurative arthritis of the hip joint, 3 of these known to be due to streptococcus, 1 patient died and each of the survivors required an operative stabilization of the joint.

Knee joint. The lower femoral metaphysis, invaded 17 times, showed 4 instances in which the knee joint was secondarily involved, resulting twice in bony ankylosis and twice in fibrous ankylosis with marked limitation of motion. Each of these patients had their initial drainage performed elsewhere. It is our belief that this complication should be prevented in most instances by proper drainage.

Ankle and tarsal joints were each invaded once with resulting spontaneous fusion.

Failure of the tibial shaft to regenerate. We have received from other clinics 2 patients who had massive involvement of the entire tibia and had had the tibial shafts resected. One patient regenerated his tibial shaft and the other failed to do so. This complication is said to occur in 19 per cent of cases in which the procedure is done.

Fracture. There were 2 patients who sustained a fracture of the upper femur at or near the epiphyseal line before coming under our care. They had not been adequately protected by brace or plaster-of-Paris during the acute stage of their disease.

Peroneal palsy. One patient whom we saw had a massive scarring of the posterior popliteal region and a complete peroneal nerve palsy. It must be assumed that his peroneal nerve was divided at one of his drainage operations.

Growth disturbance. Nine patients showed shortening of a leg: 3 under 1 inch, 4 between 1 and 2 inches and 2 from 2 to 3 inches.

One patient with a complete recovery of function following a

primary streptococcus arthritis of his knee had an increase in length of the involved leg of about ¼ inch.

End Results

We fortunately know the end results in 54 of our 56 patients, a follow-up of over 96 per cent. We have classified our patients as *healed*, with or without disability; and *unhealed*, with or without disability. By disability we mean ankylosis of a joint, shortening of an extremity, limp, pain, etc.

Three patients have died, of our 34 seen during the acute stage. Two of these had acute staphylococcus sepsis and one, an infant, had streptococcus infection of the hip. Each died at about 1 week after onset. This gives a mortality of 8.8 per cent among our acute cases of hematogenous osteomyelitis and arthritis.

OF THE 51 KNOWN SURVIVORS, THE END RESULTS ARE AS FOLLOWS

	Without disability		With disability		Total Patients
	No. of patients	Per cent	No. of patients	Per cent	
Healed	26	51	12	23.6	38
Unhealed	5	9.9	8	15.4	13
Total Patients	31		20		51

The 13 patients who are rated as unhealed include 3 at present under treatment. It will be seen that though about 75 per cent of the patients are healed, only a little over half of the patients are healed without some disability.

Conclusions

1. Our experience in hematogenous acute osteomyelitis and arthritis simply offers corroboration on a small scale of many facts that have been previously noted. It is a disease of childhood and adolescence with males more frequently involved than females.

2. The bacteria responsible have been staphylococcus in nearly 80 per cent and streptococcus in most of the remainder. There seems to be a selective action on the part of these two bacteria, staphylococcus in the main affecting the bone primarily; and if a joint is invaded, it is by extension. Streptococcus tends to invade the joints primarily and predominates in infants.

3. The bones and joints of the lower extremity and other weight-bearing bones or joints are much more frequently invaded than those of the upper extremity. Of the long bones, the femur was most frequently invaded in this series.

4. Approximately 30 per cent of these patients had more than one focus of infection. A secondary invasion into the hip joint invariably has followed a focus in the upper femoral metaphysis. The knee joint in this series has been involved in 23.5 per cent of the cases involving the lower femoral metaphysis, and we feel that this may be unnecessary.

Growth disturbance ensued in about 17 per cent of those cases involving the lower extremities.

Fractures of diseased bones may be avoided by adequate protection with a plaster-of-Paris circular splint.

5. Approximately 75 per cent of our surviving patients have healed but almost a third of these have disability. Our mortality was 8.8 per cent of the 34 patients seen in the acute stage of their disease.

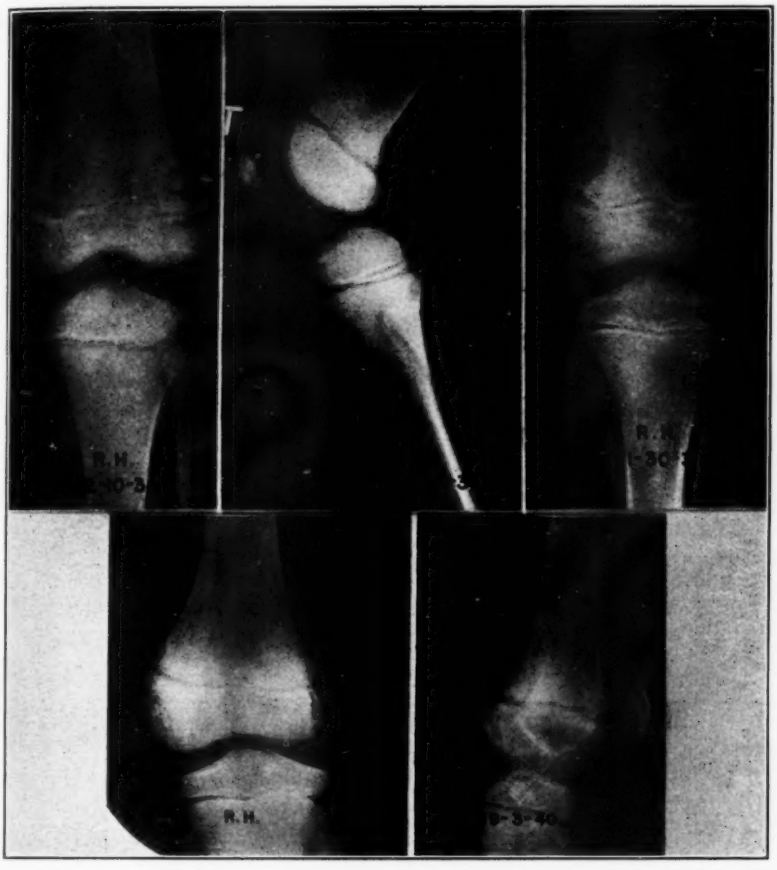
6. Our treatment of these patients seen in the acute stage of their disease is supportive: Infusions, transfusions, morphine and protection of the involved extremity. When we are satisfied that there is suppuration, rapid drainage through small carefully placed incisions with minimal trauma followed by immobilization with circular plaster-of-Paris splints offers, we feel, the best treatment.

REFERENCES

1. Wilensky, Abraham O.: *Osteomyelitis, its pathogenesis, symptomatology and treatment.* New York, Macmillan, 1934.
2. Beekman, F. and Sullivan, J. E. Blood-borne pyogenic infections of bones and joints, *Ann. Surg.*, 1940, *111*:292.
3. Kennedy, Robert H. Osteomyelitis in compound fractures, *Am. J. Surg.*, 1937, *38*:327.
4. Phemister, D. B. Pyogenic osteomyelitis, in *Nelson new loose-leaf surgery*, 1940, v. *3*, chapt. 7.
5. Starr, C. L. Osteomyelitis, in *Practice of surgery* (Lewis), 1927, v. *2*, chapt. 2.
6. Key, J. A. *Personal communication.*
7. Wilson, J. *Personal communication.*
8. Ryerson, E. W. *Personal communication.*

FOR CASE ILLUSTRATIONS, SEE PAGES 216-220

Case 1—R. L., St. Luke's No. A 10582, male, 19 months of age. He was admitted to St. Luke's Hospital March 31, 1937. About one month prior he had a cold and sore throat, and two weeks prior he had swelling of the left knee and fever. His temperature on admission was 104 degrees, white blood cells 80,000. Blood culture was negative. The patient showed effusion into the knee joint and very marked tenderness around the knee. It was not possible to be entirely certain whether this was suppurative arthritis or osteomyelitis involving the lower femoral metaphysis. On incision and drainage, drill holes were placed in the lower femur and upper tibia but no pus was found. However, the knee joint showed 20 cc. of pus which on culture was proved to be hemolytic streptococcus. The knee joint was drained by medial and lateral parapatellar incisions. A cast was applied and the patient was given sulfanilamide. His temperature fell to normal on the 16th day. The wound was entirely healed in 2½ months after operation. He was allowed to bear weight a week later. The roentgenogram of March 31, 1937 shows very definite distention of the capsule with no definite evidence of any involvement of the upper tibial or lower femoral metaphysis. That of June 25, 1937 still shows capsular distention and thickening. Those of June 20, 1940 show definite healing with a wide joint space and little or no disturbance of the femoral epiphysis. His latest follow-up, 3 years after operation, shows no limp, a full range of motion in his leg, and the left leg is ¼ inch longer than the normal leg. This is a very fortunate outcome in acute streptococcus arthritis of the knee joint in an infant.



Case 2—R. H., St. Luke's No. A 6792, male, 8 years of age. He was admitted to St. Luke's Hospital December 9, 1938, 2 weeks after pain began in the left knee. He had no history of trauma or previous infection. Temperature was 104 degrees and white blood cells 14,400. Blood culture showed hemolytic staphylococcus. On December 19, 1938 an incision and drainage of the lower femoral metaphysis was performed through a trap cut in the bone. A plaster-of-Paris dressing was applied. He remained 54 days in St. Luke's Hospital. He was entirely healed in 4 months. The roentgenograms of December 10, 1938, antero-posterior and lateral, show involvement of the lower femoral metaphysis. The roentgenogram of January, 1939 shows the trap which has been removed from the femur, and those of September, 1940 show healing of the lesion. In September, 1940, nearly 2 years after onset, he has a full range of motion in his knee joint and hip joint, and his legs are of equal length. He has no additional focus. To date this has been a perfect result. This is a single lesion with a single operation, and he is healed without disability.

Case 3—C. W., St. Luke's No. 107-038, male, 56 years of age. Following a prostatectomy October 1, 1933, the patient ran a high temperature with localized infections, abscesses on his arm, phlebitis of the leg, etc. Blood culture was positive, Streptococcus angiosus. Within a month he began to complain of pain and stiffness in the small of the back, and by March, 1934 these "lumbago" pains had become very acute. The x-rays of the spine taken in March, 1934 showed a definite destructive lesion in the first and second lumbar vertebrae. His pain continued and by the latter part of November he had developed a large right psoas abscess which was incised and drained at St. Luke's Hospital. Following the operation a tiny sinus continued to discharge for 8 to 9 months and then healed. The lateral roentgenogram of the lumbar spine of March, 1934 shows a definite suppurative disease of the first and second lumbar vertebrae. The roentgenograms of October, 1934, antero-posterior and lateral, show progressive involvement of these two vertebrae with an enormous psoas abscess. The roentgenograms of March, 1938, lateral view, shows healing with some spontaneous fusion of the involved vertebrae.

Case 4—L. B., St. Luke's No. 111-080, male, 14 years of age. This patient gave a history of severe pain in the left knee with marked swelling and high fever following a long horseback ride. He was seen by two physicians who made a diagnosis of acute rheumatic fever. The patient had a systolic heart murmur. I saw the patient when his symptoms were subsiding and he was in his home without x-rays. I asked to have these taken but for some reason they were not taken. The patient within a month had a very nearly complete range of motion in his left knee. The first roentgenograms taken in February, 1926, 5 months later, showed very definitely that the patient had had an acute suppurative osteomyelitis of his femur. From 1925 through 1935 the patient has had about 10 small abscesses which have been incised and a number of small sequestra have been removed from the superficial tissues. This patient has played football and hockey all the way through college, and when last seen, 15 years after onset, he was healed. He had a full range of motion in his knee joint, and there has been no growth disturbance. The roentgenogram of February 21, 1926, shows rather massive involvement of the lower metaphysis of the left femur, and the roentgenogram of June, 1934 shows marked recalcification and healing with apparently one or two sequestra still in the femur. This patient is shown because of his original diagnosis of acute rheumatic fever, an error which, fortunately, was not disastrous.

Case 5—K. C., St. Luke's No. A 01784, male, 8 years of age. He was admitted to St. Luke's Hospital June 22, 1936. The patient had a stye 2 weeks prior to admission and 4 days prior he developed pain in his right hip. He showed marked pain, tenderness and spasm in the hip joint. His temperature was 104 degrees and white blood cells 13,186. Blood culture was positive, hemolytic staphylococcus aureus. The hip joint was aspirated and a large amount of thick yellow pus evacuated. An incision and drainage was done with drill holes in the neck of the femur. A plaster-of-Paris spica was applied. Culture of the pus showed hemolytic staphylococcus aureus. A sequestrectomy was done on October 5, 1936, incision and drainage on April 16, 1938, hip fusion on October 28, 1938, and incision and drainage on December 22, 1938. The roentgenogram of June 12, 1936 shows no evidence of involvement of the upper femoral metaphysis. The roentgenogram of September 18, 1936 shows very definite involvement of the upper femoral metaphysis, a small sequestrum and marked thinning of the hip joint space. The final roentgenogram, September 3, 1940, shows the hip joint solidly fused in excellent position, no evidence of any sequestrum. There is no evidence of atrophy. This patient has been bearing weight quite steadily and is now healed.

THE PREVENTION AND TREATMENT OF INFECTION IN WOUNDS BOTH OPERATIVE AND ACCIDENTAL*

FRANK L. MELENEY

Associate Professor of Clinical Surgery, College of Physicians and Surgeons
Columbia University

INTRODUCTION

THE title of this paper calls for a discussion of rather wide scope dealing with two more or less distinct and fairly complicated problems, namely, infection in operative and in accidental wounds; and yet they are related and in some respects they run parallel with one another. In both, of course, we are dealing with wounds contaminated with bacteria. On the one hand, we have built up an elaborate system fairly generally followed throughout the so-called civilized world, called "sterile technique," designed as a prophylactic against operative wound infection. On the other hand, not anticipating accidents, no effort is made to prevent bacteria from gaining admission into the tissues at the time of an accident. The prophylaxis is directed at preventing those organisms from gaining a foothold in the body after they have entered the wound.

Operative wounds occur in both normal and debilitated individuals with the latter probably outnumbering the former. Accidental wounds occur more often in healthy rather than debilitated people. In operative wounds there is, or should be, relatively little trauma to the tissues but the wound is exposed to contamination for a relatively long time. In accidental wounds there is frequently extensive trauma to the tissues but there may be only a brief period during which organisms enter the wound. In operative wounds under ideal conditions the organisms which are introduced are few in number and of low virulence. In accidental wounds the organisms which get in are many and may be of high virulence. In operative wounds the foreign bodies which are introduced are for the most part sterile. In accidental wounds the foreign bodies are

* Presented October 16, 1940 in the Graduate Fortnight of The New York Academy of Medicine.

usually highly contaminated. Operative wounds occur when the various physiological processes of the body are being considerably disturbed, circulation, alimentation, respiration, urination, fluid, protein and electrolyte balance, and so forth. Accidental wounds occur when most of the body functions are normal. Both operative and accidental wounds are frequently accompanied by varying degrees of shock or hemorrhage or both. All of these things have some bearing on the development of wound infection and on the measures we may take to prevent or treat such infections. In the case of operative wounds the surgeon has the situation more or less under his control from beginning to end and the percentage of infections is low with a comparatively low death rate. With accidental wounds the surgeon can only begin to control the situation after the patient comes to him and any delay generally increases the incidence of infection and raises the death rate.

The question which we have to face this evening is, how can operative wound infection be brought down to the irreducible minimum and how can the incidence of accidental wound infection approach this same figure? In other words, can we further control the development of operative wound infection? Is there any way to bring accidental wounds under prompter and better control? This paper will endeavor to present the pros and cons of these two questions.

Operative Wound Infections

Recent reports in the medical literature indicate that this important problem is being studied by a number of individuals in different clinics. In almost every instance such a study is initiated because of some catastrophe or some unexpected incidence of wound infection and each author emphasizes one or another factor in the problem, often to the exclusion from consideration of the other factors.

Every hospital has its own rules for sterile technique and these are largely based on a few fundamental principles laid down by Pasteur and Lister sixty or more years ago. Before that time it was fully expected that every operative wound would become infected. After that time postoperative infections began to disappear until now we expect operative wounds in clean cases to heal without infection. Sterile technique that is handed down from generation to generation by staff surgeons or surgical residents frequently becomes modified from year to year either consciously or unconsciously. The occurrence of an unexpected wound

infection may arouse the surgeon to seek some explanation for the incident in that individual case or it may cause him to check up every step in the sterile technique in his own hospital. This may even lead to some experimental studies in those fields where perfect sterility has not yet been obtained. Wherever such a study is first started, the incidence of infection is usually found to be high but if the study goes on and the interest of the staff is maintained, the incidence goes down even if the weak spots in the technique can not be definitely proven. The staff becomes "wound infection conscious," little breaks in technique are promptly noticed and corrected and the doors through which contamination may come are gradually closed.

Contamination of the Wound

What are the principal sources of bacterial contamination of operative wounds? We can look at this question from two points of view to find the answer. First, we can determine what organisms are found on culture when an infection develops and search the operative surroundings for similar organisms. Secondly, we must consider everything which comes in contact with the sterile field to be a potential carrier of organisms.

In a large series of postoperative infections it is found that Staphylococcus albus is the most common organism. This is usually associated with the mild or trivial infections. In the serious infections we find the Staphylococcus aureus and the hemolytic streptococcus, the nonhemolytic streptococcus, the Bacillus coli, and more rarely the Bacillus pyocyaneus, anaerobic streptococcus and Clostridium welchii. Where are these organisms found in the neighborhood of the operative field? First of all, the skin of the patient, of course, may have on its surface any organism; but even when it has been thoroughly washed with soap and water, ether and alcohol and painted with an antiseptic, if bits of skin are taken for culture, the Staphylococcus albus is almost invariably found and occasionally the yellow staphylococcus. No skin antiseptic has yet been found which will penetrate the pores of the skin sufficiently to destroy all of the organisms harbored there. However, such cleansing should be done and skin antiseptics should be used to bring down the number of organisms to a minimum. Tincture of iodine has been time honored as a skin antiseptic and although others have been recommended and are frequently used, in our researches they

have fallen short of iodine in the percentage of negative cultures when bits of skin are taken for culture. This is one vulnerable spot in our sterile technique and one which should be strengthened. After the incision is made towels clipped to the skin edges will minimize the entrance of organisms discharged from the pores to the surface of the skin during the course of an operation.

But where do the hemolytic staphylococci and hemolytic streptococci come from that are found in the more serious operative wound infections? The chief source of these is unquestionably the noses and mouths of the people in the operating room. Coming as they do from a condition of active growth in a human environment, if they are discharged directly into the wound from the unmasked nose of any member of the operating team, they find themselves in a favorable environment similar to that from which they came and they lose no time in continuing their rapid multiplication. These organisms are no respectors of persons; they lodge in the noses and throats of the professors of surgery as well as the junior member of the team, the nurses, anesthetists, orderlies and the visitors who so frequently peer over the shoulders of the operators. There is no excuse whatsoever for anyone entering an operating room either during an operation or at any other time without adequate masking of both the nose and throat. It was proven beyond the shadow of a doubt by culture and by cross absorption of agglutinin tests that a hemolytic streptococcus causing a serious wound infection in a patient was identical with a hemolytic streptococcus harbored in the unmasked nose of the sterile nurse who was on the operating team when the operation was performed.[1]

Now what is an adequate mask? A four ply fine meshed muslin gauze will catch the droplets but some organisms not contained in droplets may pass through or around such a mask. An impermeable mask, with a rubber, cellophane or paper membrane incorporated in the gauze will prevent the direct passage but will increase the number of organisms which are carried around the impermeable layer. Such masks may be incorporated into a helmet of fine meshed gauze which can extend down into the sterile gown. Such a mask will not only prevent particles falling from the hair or neck of the operator but will divert air currents down into the gown. It may feel a little uncomfortable when first worn but habitual use will soon make the wearer unaware of it and it will reduce contamination from this source to a minimum. The perfect mask which

will stop completely all organisms from this source has not yet been found. Further precaution should be taken by any operator to minimize conversation during an operation, for unquestionably more organisms are cast out during speech than during quiet breathing.

The hands of the members of the operating team may be another source of virulent hemolytic staphylococci or streptococci or the intestinal organisms including the "gas bacillus," particularly if they have recently dressed patients with such infections. These organisms may be transferred to the hands by handkerchiefs from the individual's own nose and throat. Scrubbing hands with scrub brush and soap under running water will remove the great majority of these organisms if the scrubbing is done thoroughly and systematically, going over the whole surface of hands and forearms and elbows with particular care to remove dirt from beneath the finger nails. Five minutes of vigorous scrubbing should be enough, a longer period may do damage by abrading the skin. An additional protection is given by covering hands and arms and cleaning under nails with a suspension of lime and soda left on for 2 to 3 minutes and then washed off with 70 per cent (by weight) alcohol. But these hands should not be considered sterile. They should be powdered before the gown is put on. Stockinette sleeves will rub off the excess powder which might fall down upon sterile gloves or on the sleeves of the gown. Gloves are then held open by the sterile nurse in such a manner that the hand can be inserted without touching the edge, for this can not be done by the operator himself with the newer anode process gloves. It can be done, however, with the older gauntlet ribbed gloves, which may be put on by the sterile nurse who is the first to scrub and then discarded after she has held the gloves of the other members of the team, one of whom may then hold fresh gloves for her. Thus may the organisms from this source be reduced to a minimum. If any gloves are torn or pierced during an operation they must, of course, be changed at once.

Another obvious source of contaminating organisms is the air. Dust particles and suspended moisture particles contain them. They are carried around the room by air currents and fall on the sterile field and sometimes directly into the wound. Culture plates placed in various parts of the room have demonstrated that anywhere from 30,000 to 60,000 viable organisms descend upon a sterile field during the course of an hour's operation.[2] Only one tenth of this number is found on plates

exposed in an empty operating room before an operation, but the number rapidly rises as soon as people come in and move around depositing organisms from their shoes and clothing. It is obvious therefore that the number of persons entering the operating room should be reduced to a minimum and they should wear sterile gowns and shoe covers. Their movements about the room should be limited and the opening and closing of doors should be cut down as much as possible. The deposit of these organisms on the sterile field may be further minimized by the use of canopies over sterile tables.

In the last few years attempts have been made to destroy these organisms by means of ultraviolet radiation. There are zones in the ultraviolet spectrum where the rays are highly bactericidal with a minimum of erythema producing effect and such zones may be selected by using the proper kind of glass for the tubes. Hart[3] has presented evidence to show that ultraviolet radiation may completely destroy air organisms with intensities not injurious to tissues. He has also shown that the incidence of infection in operative wounds in cases operated upon under these rays, is considerably reduced as compared with a previous control series. Furthermore, the postoperative temperature curves in such patients are lower than in control cases even without infection. In our laboratory Kraissl[4] with the technical assistance of engineers from the Westinghouse Company has devised a series of ultraviolet tubes incorporated in a circular illuminating unit with a central vent. The heat of the lamp causes convection currents to ascend through the lamp and carry the bacteria laden particles past the most intense focus of the ultraviolet rays which is about a foot above the wound. Such tubes emit rays in the bactericidal zone with intensities sufficient to kill the great majority of suspended bacteria over the sterile field. Independent wall units are employed to cover the areas surrounding the operating table. The intensities used are within the safety zone as far as injury to the tissues go and the intensity may be automatically reduced during the course of the operation, while it may be stepped up as the tubes begin to show evidence of losing some of their strength in the course of time. We have had such an installation in one of the operating rooms at the Presbyterian Hospital for the past few months and are ready to make a preliminary report to the effect that all clean operations which have been performed under it have resulted in clean wound healing without exception. "Clean-contaminated" wounds in regions which are uninflamed at the time of

operation but which become contaminated by bacteria from neighboring tissues during and after operation have shown a much lower incidence of wound infection than control series. We have not been able to completely sterilize the air with intensities which we consider safe but we have reduced the number to approximately 10 per cent and the wound healing figures, although it is a small series, seem to be significant, and warrant the continued use of this additional safeguard.

With regard to catgut and the ligature and suture material, conditions have greatly improved in the last ten years. Now, the new Pure Food and Drugs Act has defined as drugs, catgut and other suture material as well as cotton, gauze bandages and all materials sold as sterile goods. The Food and Drugs Administration of the Department of Agriculture has been given responsibility for setting up a continuous control by means of the periodic examination of goods bought on the open market and by the confiscation of goods not meeting the standards. The United States Pharmacopoeia with the help of a "Sterile Products Advisory Board" has set up standards and stipulated certain tests for sterility. These standards will begin to operate on January 1, 1941, and it is hoped that unsterile catgut will disappear from the market forever.[5]

This brings us to the last category, namely, the instruments and utensils, the linen goods, the cotton, the gauze, the sponges, the compresses, towels and sheets, namely, everything which goes into and comes out of the water sterilizers and the autoclaves. Everything that has gone before must be considered contaminated in spite of all of our efforts to reduce the contamination to a minimum. Instruments and dry goods can be and should be made absolutely sterile. But I am sorry to say they are not always sterile, either because of faulty apparatus or the faulty use of good apparatus. With regard to the instrument and utensil sterilizers, precautions must be taken with the plumbing to use traps in the drainage pipes which will prevent the reflux of sewage water at the end of sterilization. Ten minute boiling will destroy all known pathogenic organisms. Although some non-pathogenic spores have been found which will survive boiling for an hour they need not be considered. This ten minute period must not be shortened to please an impatient surgeon calling for an instrument which was not ready. Walter has devised a rapid autoclave for instruments in which they are washed and sterilized at the same time in a much shorter period of time.[6]

Sharp instruments like knife blades, scissors and needles, which be-

come blunt by boiling, can be sterilized in 15 to 20 minutes by soaking in Bard-Parker germicide or its equivalent.

The autoclaves should have both pressure and temperature gauges with self-recording mechanisms and charts. There should be a stop cock to let out the air at the bottom of the chamber during sterilization. Doubly wrapped packages should be prepared and drums should be loosely packed so that air pockets will not be retained within them. Gloves should not be folded or placed in the autoclave with fingers down for fear that air may be pocketted in finger tips. Similar objects should be so packed that the air may be displaced downward out of them as the steam enters. An important safeguard is the preliminary evacuation of air with a vacuum of minus 10 cm. of mercury for 15 minutes. We have found that if this is done the sterilizing time may be shortened to 30 minutes, although 45 minutes gives a wider margin of safety. Without the vacuum, sterilization may not be effected for an hour or more.[2] Commercial indicators are not reliable to demonstrate that sterilization has been satisfactorily accomplished. Resistant spores of non-pathogenic organisms (B. subtilis or B. sporogenes) incorporated in cotton threads and doubly wrapped in muslin should be employed as indicators. They should be placed in a package near the air vent and sent to the laboratory for culture when the autoclaves are opened. With such precautions and with conscientious technicians I believe that we should be sure of absolute sterility in our autoclaved materials.

Contamination of Other Tissues

We have so far considered the sources of bacterial contamination of the wound at the time of operation. We must also consider briefly the contamination of other regions in the patient during and just after operation. First of all, the respiratory tract during anesthesia becomes contaminated by mouth organisms ordinarily discharged by the normal functioning of the cough reflex. These organisms frequently establish themselves in the lungs and cause a postoperative pneumonia. This contamination may be minimized by retaining the cough reflex whenever possible and by the suction of any excess of mucus during the course of anesthesia. Occasionally during the induction, but more often at the end of anesthesia the patient vomits and aspirates this material. This is a frequent cause of the more serious forms of pneumonia and occasionally results in lung abscess. The withholding of food before operation

and the usual precautions during these phases of anesthesia should minimize the occurrence of this accident. If vomiting does occur a dependent position of the head, suction and the returning cough reflex may prevent too much aspiration.

If voiding is impossible and catheterization has to be resorted to, organisms are almost invariably introduced into the bladder because of the impossibility of sterilizing the urethra. Infection should not occur unless catheterization is repeated many times and the bladder is permitted to distend unduly or not empty completely.

Hypodermic and intramuscular injections which are frequent after operations are occasionally the agents of infection if the proper precautions are not taken to sterilize syringe and needle and the skin at the site of injection.

The Establishment of Infection

The development of an infection within the body depends not only upon the introduction of organisms into the tissues but upon the local conditions within those tissues and in the body as a whole which favor or retard the establishment of colonization of these organisms. In certain animals and probably in humans, the introduction of a single virulent organism may result in an infection and death. On the other hand the introduction of millions of less virulent organisms may produce no infection whatever. The outcome depends upon the relative strength of the offensive forces of the organisms and the defensive forces of the body.[7]

Certain measures may be taken by the operator to minimize the development of infection in a wound which becomes contaminated under our so-called sterile technique. The most important of these is minimizing trauma. Sharp cutting should be used in making incisions and dissections, retraction should be gentle, artery clamps should not seize masses of tissue. Hemostasis should be complete. Fine silk should be used for ligatures and sutures in all clean cases. Since 1930, when we began silk technique in steadily increasing numbers of clean cases, every year has demonstrated a lower incidence of infection with silk as compared with catgut. If there is an established infection or gross contamination, fine catgut should be employed—never heavier than size 0. The maximum blood supply should be conserved. No tension should be used which will cut off blood supply. All old blood and cellular debris should

WOUND HEALING—CLEAN CASES 1925-1939

Year	Cases	Percentage		
		Total Inf.	Triv. Inf.	Ser. Inf.
1925	558	14.0%	10.0%	4.0%
1926	581	15.0	11.0	4.0
1927	653	15.0	12.0	3.0
1928	640	11.0	9.0	2.0
1929	771	9.0	7.0	2.0
1930	747	10.0	7.0	3.0
1931	950	7.1	5.4	1.7
1932	1053	5.3	4.2	1.1
1933	1132	4.8	3.6	1.1
1934	1279	3.7	2.8	.9
1935	1417	3.1	2.5	.6
1936	1558	3.1	2.5	.6
1937	1614	2.2	1.4	.8
1938	1668	2.1	1.6	.5
1939	1725	2.6	2.0	.6

be washed out of the wound before final closure. Ether may be used for this purpose. Before closure, the introduction of potent staphylococcus bacteriophage or sulfanilimide powder has been advocated but with the incidence of infection already low with the above precautions, these procedures are not at present advisable. A continuous study of wound infections is of great importance in reducing the incidence. It keeps the staff "infection conscious." Everyone tries to lower the figure and weak spots in the technique are strengthened. Our figures for the last 15 years bear this out.

Clean-Contaminated Cases

So far we have been speaking of the prophylaxis of wound infection in clean cases. There is another large group of operative cases in which there is no established infection but the wound becomes contaminated immediately because of our inability to sterilize the surface, even approximately, or because of the proximity of contaminated regions, or because the operative incision passes through normal tissues into an infected cavity or viscus. Such operations are those performed on or near the mouth or the vagina or rectum. In this group are acute appendicitis cases which are not drained, all gallbladder, stomach and intestinal

operations. In this group also we have included accidental wounds, such as compound fractures, in which the region has been contaminated and an operative procedure is necessary. We call these cases "clean contaminated" and do not expect as perfect wound healing as in clean cases. For example, in 1939 we had a total of 2.6 per cent of infections in 1725 clean cases. Of these 0.6 per cent were serious. In the same year we had a total of 8.7 per cent of infections in 866 clean contaminated cases of which 2.1 per cent were serious. In the prophylactic treatment of these wound infections all of the measures which we use in clean cases should apply. In certain cases drains should be used. In heavily contaminated cases the skin and subcutaneous tissues should be left open. But in this group we have an added responsibility. We must try to prevent the growth of organisms which we know have grossly contaminated the wounds. Zinc peroxide should be applied where anaerobic organisms are known to be involved, as around or in the mouth, or around ostomies of the large bowel, or around the anus, or in the vagina after perineoplasties, and after perineal resections, hemorrhoids, fistulae and pilonidal cysts. As a prophylactic against infection of the peritoneal cavity after appendicectomy or abdominal resections of the bowel, Steinberg[8] has advocated in recent years the use of rapid vaccination of the cavity with colon bacilli suspended in gum tragacanth. This has yielded favorable results in reported cases but more recently the use of the sulfonamide group of drugs has been so encouraging in the hands of Lockwood and Ravdin[9] and others including our own clinical and laboratory experiences not yet reported, that they warrant further clinical trial and if possible extensive experimental investigation. Particularly encouraging in compound fractures are the results in two fairly large series of cases in Baltimore treated by Bennett and Long[10] with general sulfanilamide and in Minneapolis by Jensen and his co-workers[11] with local application of the drug. The lack of adequate bacteriology in these series makes it uncertain just what organisms responded favorably and which failed to respond, but gas gangrene was absent in all of these cases. In a smaller series of 18 compound fractures treated by Pulaski, 15 were left open and dressed with zinc peroxide without an infection. Three were closed and became infected. These wounds were opened and were treated with zinc peroxide and the infection ceased. A control series of 19 patients treated during the same period had 5 infections, including 1 case of gas gangrene developing in a stump closed after amputation. This small

series suggests that this drug also may be effective in preventing infection in compound fractures. Further extensive clinical trial checked by adequate laboratory work will have to be done before these newer methods can be properly evaluated.

Accidental Wounds

An accidental break in the surface covering of the body carries into the wound organisms which were on the surface and others which were on the object causing the wound. Frequently also street dirt or garden soil or clothing are carried in, bearing bacteria and in some instances chemicals more or less irritating. Such wounds occur usually in healthy individuals who are moving around and bumping into other people and things. Not infrequently a fist crashes into a set of teeth with disastrous results.

In industry, to be sure, safeguards are placed on machinery to minimize accidents. Frequent washing of hands is encouraged to reduce the entrance of bacteria and dirt if accidents occur, but accidents are never really expected and, so far as I know, no serious effort is made to prevent organisms from getting into a wound primarily at the time of accident. Of course, secondary contamination is another matter. Thoughtless individuals may wipe away the blood with an unsterile cloth, or an article of clothing, or they may suck the wound or they may apply some household remedy and thus secondarily contaminate the wound.

Accidental wounds may range from a tiny pin prick or scratch which does not draw blood to an extensively comminuted fracture with extremely damaged muscle. Minor wounds are usually cared for by the patient himself until the wound is healed or until an infection gains a foothold when he may put himself in the hands of a doctor. With major wounds, particularly those with much loss of blood or functional disability, the patient goes promptly to the doctor. In industrial groups with medical supervision, the injured man goes to the doctor for the most trivial as well as the most serious injury. Thus, the surgeon has an opportunity to use all of his knowledge and ingenuity to prevent further injury, eliminate the threat of infection and favor rapid healing with restoration of form and function. What should the surgeon do when an injured patient comes under his care? He must assume that all accidental wounds are contaminated. He must try to anticipate what organ-

isms are present in order to give the best primary treatment and he must know as soon as possible exactly what organisms he has to deal with. To be specific let us say that a nurse has pricked her finger with a pin while dressing a patient. The surgeon finds out the nature of the patient's infection—a hemolytic streptococcus empyema. He knows that any medication applied locally will not reach any inoculated organisms. Shall he cut out the wound or be conservative? I believe that he may safely be conservative, depending upon sulfanilamide to fortify the patient against infection, even if the inoculation has entered a tendon sheath. Soaking the finger at frequent intervals in water at 110° F. will favor resolution of the process. But the surgeon must watch for the earliest indication of inflammation and if it develops be ready to go in and establish drainage.

An easier decision may be made when the accidental wound is a laceration of the soft parts following a street accident. In this situation the intelligent surgeon must anticipate the presence of anaerobic organisms including tetanus and gas gangrene. Immediate operation is required. The patient is prepared under regional block or general anesthesia. If there has been considerable bleeding a tourniquet should be applied but not left on for more than 20 minutes for the upper extremity, or 40 minutes for the lower extremity, without being released. The wound is then protected by gauze while the neighboring skin is thoroughly cleaned with soap and water or benzene followed by ether and 70 per cent alcohol. The margins and surfaces of the wound should then be cut away leaving grossly normal tissues on all surfaces. All foreign bodies must be removed. (All of the debrided tissue and foreign bodies should be taken in a sterile receptacle to the bacteriological laboratory for a complete bacterial analysis by aerobic and anaerobic methods.) I cannot too strongly impress upon you the importance of this. If any tendons or nerves have been severed they should be carefully approximated with fine silk. Hemostasis should be complete—catgut ligatures should be applied to vessels so as to include only a minimal amount of the surrounding tissue. After debridement the wound should be irrigated with large quantities of normal saline.

Now the question arises, shall the wound be closed with or without drainage or shall it be left open? If the operation is done within 6 hours of the time of the accident, the surgeon will have to use his own judgment based upon his knowledge of the conditions of the accident, the

age and general health of the patient, the degree of tissue damage and the extent of the debridement. The wound may be closed without drainage if it is dry and shallow. A small Penrose tube should be inserted if it is deep or moist. A thin layer of sulfanilamide powder may be laid over the wound surfaces before their approximation. If this is done, drainage should not be used. Sulfanilamide should also be given systemically. The patient should be tested for serum sensitivity and if he is not sensitive, he should receive 3000 units of tetanus antitoxin and one therapeutic dose of polyvalent anti-gas gangrene serum. In 24 hours the cultures should reveal most, if not all, of the organisms with which one has to deal. A closed wound puts a burden of responsibility upon the surgeon, for he must watch carefully for the first evidences of infection and if they appear, he must decide by the severity of the signs and the nature of the organisms whether or not to open the wound again. If a Staphylococcus albus is present, the wound may be left closed unless the signs become pronounced. If a Staphylococcus aureus is present, the wound should be opened if more than minimal signs develop. Potent bacteriophage will help to control the infection. If a hemolytic streptococcus is present, the wound may be left closed unless signs become marked. If anaerobic streptococci or Welch bacilli are present, the wound should be opened and zinc peroxide applied.[12, 13] If there is a mixture of organisms present, there is still greater indication than for a single species for opening a wound which has been primarily closed.

If the debridement is done more than 6 hours following the accident, sulfanilamide should be given systemically and the wound should be left open. Then the surgeon must decide what to apply as a dressing—fine meshed vaseline gauze to be left without change or sulfanilamide powder or zinc peroxide. We do not know as yet what is best. This question should to be subjected to an extensive clinical experiment carried on in several different hospitals. For the present I would personally prefer zinc peroxide for the first dressing until the cultures are heard from, because of the frequency of anaerobic contamination in accidental wounds. If no anaerobes or hemolytic streptococci are found, it may be discontinued and vaseline gauze or China silk with normal saline applied. If staphylococci are found, I would test them for susceptibility to a potent bacteriophage and apply that on China silk once or twice daily. If hemolytic streptococci are found, I would either continue zinc peroxide or change to sulfanilamide. If E. coli or a mixture of aerobes are present,

sulfanilamide is the dressing of choice, although a potent phage might be more effective against the colon bacillus.

In the treatment of compound fractures there seems to be a difference of opinion at present and this question likewise should be subjected to a well controlled clinical and bacteriological study. I have already referred to the work of Bennett, Jensen and Pulaski in speaking of clean-contaminated wounds.

Trueta's method of treating compound fractures, which he used in Spain, has stimulated wide interest and its favorable results have been reported from England.[14] He practiced extensive debridement of the wound and applied dry gauze dressing and fixation in plaster without a change of dressings for several weeks. In over 1000 cases only 8 per cent became infected with one case of gas gangrene and only one death—a truly remarkable series. The end results of this treatment have not yet been reported but from a primary infection standpoint it is extremely encouraging. Whether these figures can be improved by the administration of sulfanilamide or zinc peroxide locally before closure or sulfanilamide by mouth will not be known until they have been tried in comparable series.

It seems probable that in civil practice the best results would be obtained by wide debridement, internal fixation, open wound, sulfanilamide by mouth and either zinc peroxide or sulfanilamide locally.

The Active Treatment of Infections

The Active Treatment of Postoperative Infections. If, in spite of all of the precautions of sterile operating room technique, a wound infection develops, active treatment to combat the infection is called for. One can tell from the local reaction as well as the general symptoms whether the infection is trivial or serious. If it is trivial, local treatment is all that is necessary. The involved portion of the wound must be opened and the pus evacuated. Deep pockets may require drainage. Cultures must be taken and appropriate specific treatment may be instituted. In the serious cases of wound infection something more active is required in the way of treatment. These infections usually occur in the first few days after operation. An unexpected temperature always requires an examination of the wound. Sometimes pulmonary signs and symptoms divert the attention and the surgeon may fail to appreciate that the wound is the cause for major concern. This is particularly

likely to occur when gas gangrene is present, giving alarming general symptoms. Usually, however, local pain calls attention to the wound. If there are signs of inflammation—swelling, redness, tenderness or crepitus—the wound should be opened to the full extent of the involved portion. A smear of the pus should be stained at once, for the morphology of the contained organisms may reveal their nature. Presumptive diagnosis by smear should, of course, be confirmed by culture. This may change the initial procedure, but treatment should be started at once and should be as specific as possible. If the organism is a staphylococcus and a potent bacteriophage is available, it should be applied daily to all parts of the wound surfaces. If it is an odorless streptococcus, probably hemolytic, sulfanilamide should be used both generally and locally.

If large Gram-positive rods are numerous, the Welch bacillus may be assumed. Further evidence of this are gas bubbles in the exudate, necrosis of the muscle and crepitation, either felt with the hand or heard with the stethoscope. The exudate may have a "mousey" odor and the skin may show slight bronzing. Such a wound should not only be opened widely but all necrotic tissue should be cut away until normal tissues are reached. Then the wound should be flooded with a suspension of zinc peroxide, the surfaces covered with a thin layer of absorbent gauze soaked in the same suspension and overlaid with cotton soaked in water—the whole dressing then sealed with vaseline gauze.

In suspected gas gangrene cases no time should be lost by waiting for the report on the culture, polyvalent gas gangrene serum should be employed, three "therapeutic" doses to start with and continuing with one therapeutic dose every 6 to 8 hours until a fall in temperature has taken place and there is some evidence of lessened toxicity. On the basis of certain encouraging clinical observations sulfanilamide may also be given by mouth in cases of gas gangrene. The actual benefit reported may be due to the effect on associated organisms, because in pure culture in experimental animals benefit from sulfanilamide therapy has not been surely demonstrated. X-ray therapy in three or more doses of 50 r has been advocated and a striking lowering of mortality has been reported.[15] We can not as yet advise treating such cases with x-ray without further evidence, for its exponent says that if x-ray is employed, sulfanilamide, serum and even surgery are all contraindicated.

Streptococci by smear and a foul odor from the exudate suggest anaerobic streptococci. These are often associated with spirochaetes and

fusiform bacilli or with Gram-negative bacilli either aerobic or anaerobic. In all such cases zinc peroxide applied locally as above described is the treatment of choice and again it may be supplemented by sulfanilamide by mouth until we know more definitely the indications for and the limitations of these sulfonamide drugs.

If an infection of any nature becomes localized and there is much slough, hypochlorite solution should be used to favor its liquefaction, either as two-hourly dressings with changes of fine meshed gauze or cotton or delivered at frequent intervals by means of a tube.

In a small percentage of postoperative wound infections a septicemia develops, the organisms usually being the hemolytic streptococcus or the Staphylococcus aureus. In the former situation, sulfanilamide treatment should be vigorously pursued with careful daily studies of blood levels, blood counts and blood cultures. Transfusions have been successfully employed when donors could be obtained whose blood showed a high opsonic index for the infecting organism.[16]

If the organism is a staphylococcus the drug of choice is sulfathiazole with the same careful observation of laboratory studies. But staphylococcus septicemia cases should have the benefit of doubly potent staphylococcus bacteriophage and its administration should not be withheld to see what the drug will do alone. It should be given in slowly increasing doses from 0.25 to 5. cc., diluted ten times in saline, at hourly intervals for the first 8 hours and then in doses increasing more rapidly in 5 cc. increments every 4 to 8 hours until the patient is receiving 75 cc. a day. If no improvement is seen in 3 days and there is no reaction, the dose should be further increased up to 150 cc. a day.[17]

In both hemolytic streptococcus and Staphylococcus aureus septicemia, the distributing focus should be found and appropriately treated surgically by incision or excision. Metastatic foci should be watched for daily and drained if localizing signs are present. Bacteriophage and the sulfonamide drugs certainly help to prevent these metastatic lesions but if they develop we have definite proof that bacteria have gained a foothold in spite of them and these foci must almost always be drained surgically. Otherwise, they will in turn become distributing foci.

In most cases, postoperative wound infection comes under control within a few days. However, the average stay in the hospital for an infected case is double that of a corresponding clean case. This is of considerable economic importance to both the patient and the hospital.

Furthermore, wound infection may completely nullify the operation, for example, an infected hernia very frequently recurs and has to be repaired again. In a few cases death ensues, but this is fortunately rare.

Postoperative pneumonia has in the past usually been relatively mild and not a serious complication. The organism is usually a pneumococcus of one of the higher numbered types. The temperature often goes up on the first or second day after operation and it may come down spontaneously in two more days. A plug of mucus may close off a bronchus and an atelectasis form with a relatively minor role played by the infection. Other cases have a more difficult time with continued fever, severe cough with purulent sputum and occasionally empyema and lung abscess or wound disruption. Postoperative pneumonia usually responds well to sulfapyridine or sulfathiazole. It is often necessary to give the sodium salt of either drug intravenously because of the necessity for withholding everything from the stomach. It has been observed that the pyridine derivative will last longer in the blood than the sodium sulfathiazole but it is more nauseating and the nausea lasts longer (4 to 5 days) than with thiazole (12 to 24 hours). Therefore, it should be given with great caution to the patient whose stomach is upset by the operative procedure itself and patients in whom repeated vomiting puts an undue strain upon the wound. Luminal helps to minimize this nausea. As in medical pneumonia the drug should be continued for several days after the fever has subsided.

Urinary infections which develop following catheterization usually yield E. coli or non-hemolytic streptococci and occasionally both together. Sulfathiazole is the drug of choice, if the patient's kidneys are normal, for it is rapidly excreted through the urinary tract. In pure E. coli infections a potent bacteriophage may clear up a cystitis or a pyelitis if it is given intravenously as well as locally.

The Active Treatment of Infection in Accidental Wounds. If infection becomes established in accidental wounds in spite of the prophylactic measures which have been employed, the methods must be changed to meet the new situation. This should be based entirely upon the results of the bacteriological study of the debrided tissue and secondary cultures from the now infected wound. The former culture will show the potential factors of infection. The latter culture will show what organisms have survived and gained a foothold in spite of the measures which the surgeon thought would be adequate at the time of

the first operation.

I have indicated above in discussing the treatment of operative wound infection the measures required for specific types of infection. The same rules apply to the established infections in accidental wounds. The general principles involved are three in number. One must be sure of, 1. adequate exposure of the infected tissue, 2. adequate contact between the infected surfaces and any local medication, and 3. adequate dosage of internal medication.

Adequate exposure of infected tissue may be obtained by the removal of any suture used to close the wound, or it may mean further incision. This should be carried to the limits of the involved area with a comfortable margin. It is better to do too much than too little. I do not fear the spread of infection as a result of extending the incision through the barrier which has been built up. If no attempt is made to close such incisions, any unnecessary incisions or any unnecessary part of an incision will be the first to heal.

Adequate contact with local medication is of great importance. If there are any nooks and crannies in the wound where the medication does not touch, the organisms may escape its action. Bacteriophage being fluid may run everywhere in the wound but it may run out again if it is not held in contact with gauze or cotton. Sulfanilamide must go into solution in the tissue juices before it can have any effect but if the wound is closed it is rapidly absorbed in 3 to 4 days, and if the wound is open, it will run out unless held in place. It may be best applied to the wound surface by means of a powder atomizer. Zinc peroxide acts best if it is kept wet. Tissue fluids will activate it but distilled water or 2 per cent polyvinal alcohol will keep it wet longer. A creamy suspension of the powder is made with about an equal quantity of fluid. This is applied to the wound surface with an asepto syringe and then a thin layer of cotton soaked in the suspension is overlaid. This is levelled off with cotton wet with water and a flat layer of wet cotton placed on top. Several layers of vaseline gauze or fine meshed gauze impregnated with zinc oxide ointment complete the dressing. It should be changed daily but may go 2 to 3 days if conditions require infrequent dressings. The dressing comes off easily and does not stick to the wound. The old material is washed off with saline irrigation and the new dressing applied as before.

Adequate systemic administration of bacteriophage is any quantity

which does not produce a reaction but does have a favorable effect in reducing temperature and clearing the blood culture. When smaller doses do not suffice, I sometimes use as much as 150 cc. a day. I cannot too strongly emphasize the fact that adequate tests must be performed to demonstrate the "double potency" of the phage against the infecting organism. To fulfill this requirement it must not only lyse the culture in fluid medium but show no growth when the lysed culture is transferred to a blood agar plate. Only if such potent phages are used will the mortality in staphylococcus septicemia be brought down materially by the use of bacteriophage.

Adequate systemic administration of the sulfonamide group of drugs is measured by the response to treatment on the one hand and the blood level determination on the other. These do not necessarily run parallel, but daily or every other day determinations should be done and the level maintained between 5 and 10 mg. per cent. This is accomplished fairly regularly with sulfanilamide by giving an initial dose of 0.1 gm. per kilo of body weight followed by 1 gm. every 4 hours. The dosage of sulfapyridine and sulfathiazole are much more variable because of marked variations in absorption and elimination rates. Blood levels are correspondingly unstable. This fact plus the danger of urinary blockage from the acetylated compounds of these drugs makes them less satisfactory than sulfanilamide except in pneumococcus infections.

Summary

In closing I would summarize this presentation by saying: In handling clean operative wounds all sources of contamination must be reduced to a minimum. In handling clean-contaminated operative wounds the kind of contamination can be predicted by the site of the operation and can usually be adequately met by appropriate measures. In handling accidental wounds a complete bacteriological analysis of the debrided tissue must be made by anaerobic as well as aerobic methods and specific treatment must be directed toward the organisms which are found to be present.

REFERENCES

1. Meleney, F. L. and Stevens, F. A. Postoperative hemolytic streptococcus wound infections and their relation to hemolytic streptococcus carriers among the operating personnel, *Surg., Gynec. & Obst.*, 1926, *43*:338.
2. Meleney, F. L. Infection in clean operative wounds; a nine year study, *Surg.*,

Gynec. & Obst., 1935, *60*:264.

3. Hart, D. Sterilization of air in operating room by special bactericidal radiant energy, *J. Thoracic Surg.*, 1936, *6*:45; and Results from November 1, 1938 to November 1, 1939 with a further report as to safety of patients and personnel, *Arch. Surg.*, 1940, *41*:334.
4. Kraissl, C. J., Cimiotti, J. G. and Meleney, M. F. Considerations in the use of ultraviolet radiation in operating rooms, *Ann. Surg.*, 1940, *111*:161.
5. Meleney, F. L. Sterile surgical supplies (Editorial), *Surgery*, 1940, *8*:848.
6. Walter, C. W. Technique for the rapid and absolute sterilization of instruments, *Surg., Gynec. and Obst.*, 1938, *67*:244.
7. Meleney, F. L., Tinker, M. B., Davis, J. S., Kraissl, C. J., Lyons, C. and Lockwood, J. S.: A Panel discussion of postoperative infections, *Surg., Gynec. & Obst.*, 1940, *71:* Internat. Abst. Surg. 403.
8. Steinberg, B. Experimental background and clinical application of Escherichia coli and gum tragacanth mixture (colibactragen) in prevention of peritonitis, *Am. J. Clin. Path.*, 1936, *6*:253.
9. Lockwood, J. S. and Ravdin, I. S. The prophylactic use of sulfanilamide in abdominal surgery, *Surgery*, 1940, *8*:43.
10. Bennett and Long. *Personal communication.*
11. Jensen, N. K., Johnsrud, L. W. and Nelson, M. C. The local implantation of sulfanilamide in compound fractures, *Surgery*, 1939, *6*:1.
12. Meleney, F. L. Zinc peroxide in surgical infections, *S. Clin. North America*, 1936, *16*:691.
13. Meleney, F. L. and Johnson, B. A. Prophylactic and active treatment of surgical infections with zinc peroxide, *Surg., Gynec. & Obst.*, 1937, *64*:387.
14. Trueta, J. *Treatment of war wounds and fractures with special reference to the closed method as used in the war in Spain.* London, Hamilton, 1939; New York, Hoeber, 1940.
15. Kelly, J. F., Dowell, D. A., Russum, B. C. and Colien, F. E. The practical and experimental aspects of the roentgen treatment of Bacillus welchii (gas gangrene) and other gas forming infections, *Radiology*, 1938, *31*:608.
16. Lyons, C. Immunotransfusion and antitoxin therapy in hemolytic streptococcus infections, *J. A. M. A.*, 1935, *105*:1972.
17. Longacre, A. B., Jern, H. Z. and Meleney, F. L. The treatment of Staphylococcus septicemia with bacteriophage, *Surg., Gynec. and Obst.*, 1940, *70*:1.

RECENT ACCESSIONS TO THE LIBRARY

"Possession does not imply approval"

Bauer, W. W. *Americans, live longer!* Indianapolis, Bobbs-Merrill, [1940], 219 p.

Berry, K. F. *A pioneer doctor in old Japan; the story of John C. Berry.* 2. ed. N. Y., Revell, [1940], 248 p.

Brotman, R. H. *Let's look at your teeth.* N. Y., Field, [1940], 277 p.

Bunting, R. W. & Hill, T. J. *A text-book of oral pathology.* 2. ed. Phil., Lea, 1940, 460 p.

Burlingame, L. L. *Heredity and social problems.* N. Y., McGraw-Hill, 1940, 369 p.

Clark, A. J. *Applied pharmacology.* 7. ed. London, Churchill, 1940, 672 p.

Commission on Standardization of Biological Stains. *Biological stains.* 4. ed. Geneva, N. Y., Biotech Publications, 1940, 308 p.

Duffus, R. L. & Holt, L. E., jr. *L. Emmett Holt, pioneer of a children's century.* N. Y., Appleton-Century, 1940, 295 p.

Finney, J. M. T. *A surgeon's life; the autobiography of J. M. T. Finney.* N. Y., Putnam, [1940], 396 p.

Frost, W. D. & Engelbrecht, M. A. *The streptococci.* Madison, Wis., Willdof, [1940], 172 p.

Getman, F. H. *The life of Ira Remsen.* Easton, Pa., Jour. of Chem. Educ., [1940], 172 p.

Graybiel, A. & White, P. D. *Electrocardiography in practice.* Phil., Saunders, 1941, 319 p.

Grossman, L. I. *Root canal therapy.* Phil., Lea, 1940, 237 p.

Gutman, J. *Modern drug encyclopedia and therapeutic guide.* [2. ed.] N. Y., New Modern Drugs, 1941, 1644 p.

Halpern, L. J. *How to raise a healthy baby.* N. Y., Prentice-Hall, 1940, 388 p.

Harris, S., Harris, S., jr. [et al.]. *Clinical pellagra.* St. Louis, Mosby, 1941 [1940], 494 p.

Harrison, P. W. *Doctor in Arabia.* N. Y., Day, [1940], 303 p.

Kopeloff, N. *Bacteriology in neuropsychiatry.* Springfield, Ill., Thomas, 1941 [1940], 316 p.

Kummer, A. *Chirurgie voor den huisarts.* Amsterdam, Scheltema, 1940, 261 p.

Lucas, (Mrs.) M. (Scott). *Elements of human physiology.* Phil., Lea, 1940, 400 p.

McDougall, J. B. *Tomography.* London, Lewis, 1940, 73 p.

Margolis, H. M. *Diagnosis and treatment of arthritis and allied disorders.* N. Y., Hoeber, [1940], 551 p.

Maynard, (Mrs.) L. & Miscall, L. *Bellevue.* N. Y., Messner, [1940], 280 p.

Mazer, C. & Israel, S. L. *Diagnosis and treatment of menstrual disorders and sterility.* N. Y., Hoeber, [1940], 485 p.

Meyer, O. *Phlebitis, the hidden cause of most leg and foot ailments.* N. Y., Savoy, 1940, 72 p.

Montague, J. F. *Broadway stomach.* N. Y., Simon, [1940], 356 p.

Munro, D. C. *Man alive you're half dead!* N. Y., Courtenay, [1940], 209 p.

Nielsen, J. M. *A textbook of clinical neurology.* N. Y., Hoeber, [1940], 672 p.

Nygaard, K. K. *Hemorrhagic diseases; photo-electric study of blood coagulability.* St. Louis, Mosby, 1941 [1940], 320 p.

Reid, W. D. *Manual of cardiology.* N. Y., Oxford Univ. Press, [1940], 364 p.

Ross, J. A. *A handbook of radiography.* London, Lewis, 1940, 126 p.

Steincrohn, P. J. *More years for the asking.* N. Y., Appleton-Century, 1940, 218 p.

Sutton, R. L. & Sutton, R. L., jr. *An introduction to dermatology.* 4. ed. St. Louis, Mosby, 1941 [1940], 904 p.

Thomas, G. I. *Dietary of health and disease.* Phil., Lea, 1940, 317 p.

Wolf, I. J. *A family doctor's notebook.* N. Y., Fortuny, [1940], 315 p.

Wright, R. B. *Hydrotherapy in psychiatric hospitals.* Boston, Tudor, 1940, 334 p.